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(54) **COMPOSES DE DIMERES DE NUCLEOSIDES ET LEURS
USAGES THERAPEUTIQUES**
(54) **L-NUCLEOSIDE DIMER COMPOUNDS AND THERAPEUTIC
USES**

AP

(57) L'invention porte sur des dimères de nucléosides dont l'un au moins des nucléosides comporte un sucre L, ainsi que sur des préparations pharmaceutiques les contenant.

(57) The invention relates to nucleoside dimers containing an L-sugar in at least one of the nucleosides and their pharmaceutical compositions.



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(54) Title: L-NUCLEOSIDE DIMER COMPOUNDS AND THERAPEUTIC USES			
(57) Abstract The invention relates to nucleoside dimers containing an L-sugar in at least one of the nucleosides and their pharmaceutical compositions.			

L-NUCLEOSIDE DIMER COMPOUNDS AND THERAPEUTIC USES**Field of Invention**

This invention relates to dinucleoside dimers and intermediates or derivative thereof useful in the synthesis of such dimers, processes for their preparation, pharmaceutical compositions containing such, and methods of using such compounds to treat various diseases, particularly cancer in mammals. More particularly it relates to L-deoxyribofuranosyl nucleoside phosphodiester dimers where the sugar moiety of at least one of the nucleosides has an L-configuration.

Background of the Invention

Modified nucleoside analogs are an important class of available antineoplastic and antiviral drugs. Currently, there are no therapeutic compounds in use that are based on dimers of these nucleoside analogs. While dimers of the naturally occurring D-deoxyribofuranosyl nucleosides are well known, dimers in which one or both nucleosides are of the unnatural L-configuration are much less known, and their use in therapy of neoplastic and viral diseases is unknown.

In the synthesis of DNA-related oligomers, types of nucleoside dimers are synthesized as part of the overall process. These dimers usually include bases from naturally occurring DNA or RNA sequences. There is much known in the art about nucleoside monophosphate dimers. Many of these compounds have been synthesized and are available commercially. However, these dimers are made from nucleosides containing a sugar moiety in D-configuration.

Reese, C.B., Tetrahedron 14 (1978) 3143 describes the synthesis of fully-protected dinucleoside monophosphates by means of the phosphotriester approach.

Littauer, U.Z., and Soreq, H. (1982) in The Enzymes, Vol XV, Academic Press, NY, p. 517 is a

standard reference which describes the enzymatic synthesis of dinucleotides.

Heikkilä, J., Stridh, S., Öberg, B. and Chattopadhyaya, J., *Acta Chem. Scand. B* 39 (1985) 657-669, provides an example of the methodology used in the synthesis of a variety of ApG nucleoside phosphate dimers. Included are references and methods for synthesis of 3'-5' phosphates and 2'-5' phosphates by solution phase chemistry.

Gait, M., "Oligonucleotide Synthesis", IRL Press, Ltd., Oxford, England, 1984, is a general reference and a useful overview for oligonucleotide synthesis. The methods are applicable to synthesis of dimers, both by solution phase and solid phase methods. Both phosphitetriester and phosphotriester methods of coupling nucleosides are described. The solid phase method is useful for synthesizing dimers.

Gulyawa, V. and Holy, A., *Coll. Czec. Chem. Commun* 44 613 (1979), describe the enzymatic synthesis of a series of dimers by reaction of 2',-3' cyclic phosphate donors with ribonucleoside acceptors. The reaction was catalyzed by non-specific RNases. The donors are phosphorylated in the 5'-position, yielding the following compounds: donor nucleoside-(3'-5') acceptor nucleoside. Dimers were made with acceptors, β -L-cytidine, β -L-adenosine, and 9(α -L-lyxofuranosyl) adenine. Also, a large number of dimers with D-nucleosides in the acceptor 5' - position were made.

Holy, A., Sorm, F., *Collect. Czech. Chem. Commun.*, 34, 3383 (1969), describe an enzymatic synthesis of β -D-guanylyl-(3'-5')- β -L-adenosine and β -D-guanylyl-(3'-5')- β -L-cytidine.

Schirmeister, H. and Pfeleiderer, W., *Helv. Chim. Acta* 77, 10 (1994), describe trimer synthesis and intermediate dimers, all from β -D-nucleosides. They used the phosphoramidite method which gave good yields.

Thus, dimers with L-deoxyribofuranosyl moieties in any position are new, as are dimers with L-ribofuranosyl moieties bonded to the 3'-position of the phosphate internucleotide bond.

5 Modified nucleoside analogues represent an important class of compounds in the available arsenal of antineoplastic and antiviral drugs. The anticancer agents 5-fluorodeoxyuridine (floxuridine), cytarabine and deoxycoformycin and the antiviral drugs
10 3'-azidodeoxythymidine (AZT), dideoxycytidine (ddC), dideoxyinosine (ddI), acyclovir, 5-iododeoxyuridine (idoxuridine) fludarabine phosphate and vidarabine (adenine arabinoside/ara A) are representative of this class of monomeric nucleoside-derived compounds which
15 are used therapeutically.

More recently, "antisense" oligonucleotide analogues with modified bases and/or phosphodiester backbones have been actively pursued as antiviral and antitumor agents. While no clinically approved drug
20 has yet emerged from this class of compounds, it remains a very active field of research. Recently, antipodal L-sugar-based nucleosides also have found application as potent antiviral agents because they can inhibit viral enzymes without affecting mammalian
25 enzymes, resulting in agents that have selective antiviral activity without concomitant mammalian cytotoxicity.

Most naturally occurring nucleosides have the D-configuration in the sugar moiety. While the chemical
30 properties of L-nucleosides are similar to those of their β -D-enantiomers, they exhibit very different biological profiles in mammalian cells and do not interfere with the transport of normal D-nucleosides. For example, β -L-uridine is not phosphorylated at the
35 5'-position by human prostate phosphotransferase, which readily phosphorylates the enantiomeric β -D-uridine. Apparently, L-nucleosides are not substrates for normal

human cell kinases, but they may be phosphorylated by viral and cancer cell enzymes, allowing their use for the design of selective antiviral and anticancer drugs.

5 Oligonucleotides based on L-nucleosides have been studied previously. Octamers derived from α - and β -L-thymidine were found resistant to fungal nucleases and calf spleen phosphodiesterase, which readily degrades the corresponding β -D-oligonucleotide. Fujimory, et al, S. Fujimory, K. Shudo, Y. Hashimoto, 10 J. Am. Chem. Soc., 112, 7436, have shown that enantiomeric poly- α -DNA recognizes complementary RNA but not complementary DNA. This principle has been used in the design of nuclease-resistant antisense oligonucleotides for potential therapeutic 15 applications.

Thus, L-nucleoside-based compounds have potential as drugs against neoplastic and viral diseases. While L-sugar-derived nucleosides and their oligonucleotides have been widely evaluated for such activities, little 20 is known regarding the biological activities of shorter oligomers such as dimers obtained by L-nucleoside substitution.

This invention comprises novel L-nucleoside-derived therapeutic antitumor agents. Novel 25 L-nucleoside-derived dinucleoside monophosphates, based on L- α -5-fluoro-2'-deoxyuridine showed a remarkably high potency activity profile in in vitro anti-cancer assays, with indications of unique mechanisms of action, including inhibition of telomerase. Therefore, 30 the L-nucleosides can serve as building blocks for new drugs with the special advantage of low toxicity.

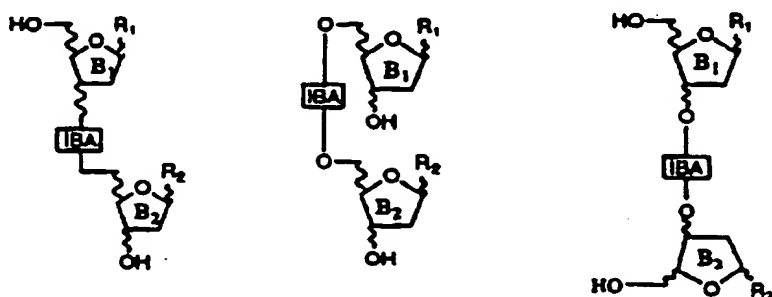
SUMMARY OF THE INVENTION

An object of the present invention is the provision of a dinucleoside dimer containing at least 35 one L-sugar.

A further object of the present invention is a method of treating neoplastic disease with a dinucleoside dimer containing at least one L-sugar.

A further object of the present invention is a provision of a pharmaceutical composition containing
5 dinucleoside dimers with at least one L-sugar.

Thus, in accomplishing the foregoing objects, there is provided in accordance with one aspect of the present invention a compound of the formulae:



10

I

II

III

15

20

25

or a pharmaceutically acceptable salt thereof, wherein A and B are each selected from the group consisting of the β -D, β -L, and the α -L nucleosides and where in at least one of A or B must be β -L or α -L nucleoside or α -L or β -L furanose sugar, R_1 and R_2 are selected from the group of bases consisting of cytosine, thymine, uracil, adenine, guanine, or inosine, 5-fluorouridine and other 5-halo uridines and wherein R_1 and R_2 can be the same or a different base or alkoxy group such as methoxy and wherein when A or B is attached to the internucleotide binding agent (IBA) at the 5' position and said A or B is β -L or α -L then the R_1 or R_2 attached to said A or B cannot be cytosine, and IBA is selected from the group consisting of phosphodiester, methoxy phospho-triesters, methylphosphonates,

phosphorodithioates, phosphorothioates, silyl ethers, sulphonates and ethylenedioxy ethers.

Specific compounds of the present invention which are effective include 3'-O-(α -L-5-fluoro-2'-deoxyuridiny)-(3'-5')- β -D-5-fluoro-2'-deoxyuridine (L-102), 3'-O-(β -D-5-fluoro-2'-deoxyuridiny)-(3'-5')- α -L-5-fluoro-2'-deoxyuridine, (L-103), 3'-O-(β -D-5-fluoro-2'-deoxyuridiny)-(3'-5')- α -L-2'-deoxyuridine, (L-107), 3'-O-(α -L-5-fluoro-2'-deoxyuridiny)-(3'-5')- α -L-5-fluoro-2'-deoxyuridine, (L-108), 3'-O-(α -L-5-fluoro-2'-deoxyuridiny)-(3'-5')- β -L-5-fluoro-2'-deoxyuridine, (L-109), 3'-O-(β -D-5-fluoro-2'-deoxyuridiny)-(3'-5')- β -L-5-fluoro-2'-deoxyuridine, (L-110), 3'-O-(β -D-5-fluoro-2'-deoxyuridiny)-(3'-5')- α -L-2'-deoxycytidine, (L-111), 5'-O-(β -D-5-fluoro-2'-deoxyuridiny)-(5'-5')- α -L-5-fluoro-2'-deoxyuridine (L-112), 3'-O-(β -D-5-fluoro-2'-deoxyuridiny)-(3'-5')-2'-deoxy- β -L-cytidine, (L-113), 3'-O-(2'-deoxy- β -L-cytidiny)-(3'-5')- β -D-5-fluoro-2'-deoxyuridine (L-114), 3'-O-(2'-deoxy- α -L-cytidiny)-(3'-5')- β -D-5-fluoro-2'-deoxyuridine (L-115), 3'-O-(β -D-5-fluoro-2'-deoxyuridiny)-(3'-5')- β -L-2'-deoxyuridine (L-117), 3'-O-(β -L-2', 3'-dideoxycytidiny)-(3'-5')- β -D-5-fluoro-2'-deoxyuridine (L-118), 3'-O-(β -D-5-fluoro-2'-deoxyuridiny)-(3'-5')- α -L-2', 3'-dideoxycytidine (L-120), 3'-O-(β -L-5-fluoro-2'-deoxyuridiny)-(3'-5')- α -L-5-fluoro-2'-deoxyuridine (L-119), 3'-O-(β -D-5-fluoro-2'-deoxyuridiny)-(3'-3')- α -L-5-fluoro-2'-deoxyuridine (L-122), 3'-O-(β -L-2'-deoxyuridiny)-(3'-5')- β -D-5-fluoro-2'-deoxyuridine (L-124), 3'-O-(β -D-5-fluoro-2'-deoxyuridiny)-(3'-5')- α -L-2'-deoxyadenosine (L-125), 3'-O-(β -D-5-fluoro-2'-deoxyuridiny)-(3'-5')- α -L-thymidine (L-126), 3'-O-(β -D-5-fluoro-2'-deoxyuridiny)-(3'-5')- β -L-5-fluoro-2'-deoxyuridine phosphorothioate (L-128), 3'-O-(β -D-5-fluoro-2'-deoxyuridiny)-(3'-5')- β -L-2'-deoxyguanosine (L-133), 3'-O-(β -D-5-fluoro-2'-deoxyuridiny)-(3'-5')- α -L-2'-deoxyguanosine (L-134), 3'-O-(β -L-5-fluoro-2'-

deoxyuridiny1)-(3'-5')-methoxy-2-deoxyribose (L-136),
3'-O-(β -D-5-fluoro-2'-deoxyuridiny1)-(3'-5')- α -L-2'-
deoxyadenosine (L-138) and 3'-O-(β -D-5-fluoro-2'-
deoxyuridiny1)-(3'-5')- β -L-1-methoxy-2-deoxyribose (L-
5 142).

More specifically, L-103, L-110 and L-117 are
found to be the preferred compounds.

Another embodiment of the present invention is a
pharmaceutical composition comprised of a pharma-
10 ceutically acceptable carrier and, a therapeutically
effective amount of at least one compound of the
present invention.

A further embodiment of the present invention is
the administration of a therapeutically effective
15 amount of the compounds of the present invention for
the treatment of cancer or viral infections.

Other and further objects, features and advantages
will be apparent from the following description of the
present preferred embodiments of the invention given
20 for the purposes of disclosure when taken in
conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic representation of the
dinucleotide dimers of the present invention.

25 Figures 2A, 2B and 3-8 are schematic
representations of the synthesis scheme followed in the
present invention. Figure 2A shows part of the
synthesis scheme for compounds of the present invention
(2'-deoxy- α -L-5-floururidene compound). Figure 2B
30 shows part of the synthesis scheme of compound N⁴-
benzoyl-2'-deoxy- α -L-cytidine, an intermediate in the
synthesis of the dimers.

Figure 3 shows the synthesis of a specific series
of alpha-beta or beta-alpha dimers.

35 Figure 4 shows the specific synthesis of an α -L-5
fluorouracil- β -D-5 fluorouracil.

Figure 5 shows an alternate pathway for synthesis of dimer compounds.

Figure 6 shows an alternate pathway for synthesis of dimer compounds.

5 Figure 7A and 7B are a schematic representations of dinucleoside phosphate dimers containing alternate backbones including methoxyphosphotriesters and methyl phosphonates.

10 Figures 8A, 8B, 8C and 8D are schematic representations of dinucleoside phosphate dimers used in the examples. Figure 8A shows a schematic representation of the dinucleotide dimers L-102, L-103, L-107 and L-109. Figure 8B shows a schematic representation of the dimers L-110, L-113, L-114 and
15 L-115. Figure 8C shows a schematic representation of dimers L-117, L-119 and L-112, Figure 8D shows a schematic representation of dimers L-115 and L-116.

20 The drawings that are not necessarily to scale, and certain features of the invention may be exaggerated in scale or shown in schematic form in the interest of clarity and conciseness.

DETAILED DESCRIPTION

It is readily apparent to one skilled in the art that various substitutions and modifications may be
25 made to the invention disclosed herein without departing from the scope and spirit of the invention.

30 The term "dimers" as used herein is defined by the structures shown in Figure 1. These compounds are L-nucleoside-derived dinucleoside monophosphates. The B₁ and B₂ units will consist of either a β -D, a β -L or an α -L nucleoside and at least one of B₁ or B₂ will be β -L or α -L. R₁ and R₂ will be the pyrimidine bases cytosine, thymine, uracil, or 5-fluorouridine (5-FUdR) other 5-halo compounds, or the purine bases, adenosine,
35 guanosine or inosine. As can be seen in Figure 1, the

dimers can be bound either 5'-3', 3'-5', 3'-3', or 5'-5'.

Specific compounds of the present invention which are effective include 3'-O-(α -L-5-fluoro-2'-deoxyuridinyl)-(3'-5')- β -D-5-fluoro-2'-deoxyuridine (L-102), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- α -L-5-fluoro-2'-deoxyuridine, (L-103), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- α -L-2'-deoxyuridine, (L-107), 3'-O-(α -L-5-fluoro-2'-deoxyuridinyl)-(3'-5')- α -L-5-fluoro-2'-deoxyuridine, (L-108), 3'-O-(α -L-5-fluoro-2'-deoxyuridinyl)-(3'-5')- β -L-5-fluoro-2'-deoxyuridine, (L-109), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- β -L-5-fluoro-2'-deoxyuridine, (L-110), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- α -L-2'-deoxycytidine, (L-111), 5'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(5'-5')- α -L-5-fluoro-2'-deoxyuridine (L-112), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')-2'-deoxy- β -L-cytidine, (L-113), 3'-O-(2'-deoxy- β -L-cytidinyl)-(3'-5')- β -D-5-fluoro-2'-deoxyuridine (L-114), 3'-O-(2'-deoxy- α -L-cytidinyl)-(3'-5')- β -D-5-fluoro-2'-deoxyuridine (L-115), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- β -L-2'-deoxyuridine (L-117), 3'-O-(β -L-2', 3'-dideoxycytidinyl)-(3'-5')- β -D-5-fluoro-2'-deoxyuridine (L-118), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- α -L-2', 3'-dideoxycytidine (L-120), 3'-O-(β -L-5-fluoro-2'-deoxyuridinyl)-(3'-5')- α -L-5-fluoro-2'-deoxyuridine (L-119), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-3')- α -L-5-fluoro-2'-deoxyuridine (L-122), 3'-O-(β -L-2'-deoxyuridinyl)-(3'-5')- β -D-5-fluoro-2'-deoxyuridine (L-124), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- α -L-2'-deoxyadenosine (L-125), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- α -L-thymidine (L-126), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- β -L-5-fluoro-2'-deoxyuridine phosphorothioate (L-128), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- β -L-2'-deoxyguanosine (L-133), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- α -L-2'-deoxyguanosine (L-134), 3'-O-(β -L-5-fluoro-2'-

deoxyuridiny1)-(3'-5')-methoxy-2-deoxyribose (L-136),
3'-O-(β -D-5-fluoro-2'-deoxyuridiny1)-(3'-5')- α -L-2'-
deoxyadenosine (L-138) and 3'-O-(β -D-5-fluoro-2'-
deoxyuridiny1)-(3'-5')- β -L-1-methoxy-2-deoxyribose (L-
142).

The term "internucleotide binding agent" or "IBA" means the backbone binding which links the nucleosides together. Although one skilled in the art will readily recognize a variety of other backbones are available and useful in the present invention. For example, see Figure 7, where methoxy phosphotriesters, methylphosphonates and phosphorothioates are shown. Although shown schematically 3'-5' the IBA's can be used to link the sugars 5'-3', 3'-5', 3'-3', or 5'-5'. In the preferred embodiment, the IBA of the compounds is either phosphodiester or phosphorothioate.

The term "antidisease" as used herein refers to any of the activities of the compounds of the present invention to affect a disease state, including antitumor, antineoplastic, anticancer, antiparasitic and antiviral activity.

A compound or composition is said to be "pharmacologically acceptable" if its administration can be tolerated by a recipient mammal. Such an agent is said to be administered in a "therapeutically effective amount" if the amount administered is physiologically significant. An agent is physiologically significant if its presence results in technical change in the physiology of a recipient mammal. For example, in the treatment of cancer or neoplastic disease, a compound which inhibits the tumor growth or decreases the size of the tumor would be therapeutically effective; whereas in the treatment of a viral disease, a agent which slows the progression of the disease or completely treats the disease, would be considered therapeutically effective.

Dosage and Formulation

The antidisease compounds (active ingredients) of this invention can be formulated and administered to inhibit a variety of disease states (including tumors, neoplasty, cancer, parasitic and viral diseases) by any means that produces contact of the active ingredient with the agent's site of action in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic active ingredients or in a combination of therapeutic active ingredients. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosages given as examples herein are the dosages usually used in treating tumors, neoplasty and cancer. Dosages for antiparasitic and antiviral applications will, in general be 10-50% of the dosages for anticancer applications.

The dosage administered will be a therapeutically effective amount of active ingredient and will, of course, vary depending upon known factors such as the pharmacodynamic characteristics of the particular active ingredient and its mode and route of administration; age, sex, health and weight of the recipient; nature and extent of symptoms; kind of concurrent treatment, frequency of treatment and the effect desired. Usually a daily dosage (therapeutic effective amount) of active ingredient can be about 5 to 400 milligrams per kilogram of body weight. Ordinarily, 10 to 200, and preferably 10 to 50, milligram per kilogram per day given in divided doses 2 to 4 times a day or in sustained release form is effective to obtain desired results.

Dosage forms (compositions) suitable for internal administration contain from about 1.0 to about 500

milligrams of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.05-95% by weight based on the total weight of the composition.

5 The active ingredient can be administered orally in solid dosage forms such as capsules, tablets and powders, or in liquid dosage forms such as elixirs, syrups, emulsions and suspensions. The active ingredient can also be formulated for administration
10 parenterally by injection, rapid infusion, nasopharyngeal absorption or dermoabsorption. The agent may be administered intramuscularly, intravenously, or as a suppository.

 Gelatin capsules contain the active ingredient and
15 powdered carriers such as lactose, sucrose, mannitol, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release
20 products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective
25 disintegration in the gastrointestinal tract.

 Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

 In general, water, a suitable oil, saline, aqueous
30 dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration contain preferably a water soluble salt of the active
35 ingredient, suitable stabilizing agents and, if necessary, buffer substances. Antioxidizing agents such as sodium bisulfate, sodium sulfite or ascorbic

acid either alone or combined are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives such as benzalkonium chloride, methyl- or propyl-paraben and chlorobutanol. Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, a standard reference text in this field.

Additionally, standard pharmaceutical methods can be employed to control the duration of action. These are well known in the art and include control release preparations and can include appropriate macromolecules, for example polymers, polyesters, polyaminoacids, polyvinyl, pyrrolidone, ethylenevinylacetate, methyl cellulose, carboxymethyl cellulose or protamine sulfate. The concentration of macromolecules as well as the methods of incorporation can be adjusted in order to control release. Additionally, the agent can be incorporated into particles of polymeric materials such as polyesters, polyaminoacids, hydrogels, poly (lactic acid) or ethylenevinylacetate copolymers. In addition to being incorporated, these agents can also be used to trap the compound in microcapsules.

Useful pharmaceutical dosage forms for administration of the compounds of this invention can be illustrated as follows.

Capsules: Capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligram of powdered active ingredient, 175 milligrams of lactose, 24 milligrams of talc and 6 milligrams magnesium stearate.

Soft Gelatin Capsules: A mixture of active ingredient in soybean oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of

the active ingredient. The capsules are then washed and dried.

5 Tablets: Tablets are prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient. 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of cornstarch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase
10 palatability or to delay absorption.

 Injectable: A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredients in 10% by volume propylene glycol and water. The solution is made
15 isotonic with sodium chloride and sterilized.

 Suspension: An aqueous suspension is prepared for oral administration so that each 5 millimeters contain 100 milligrams of finely divided active ingredient, 200 milligrams of sodium carboxymethyl cellulose, 5
20 milligrams of sodium benzoate, 1.0 grams of sorbitol solution U.S.P. and 0.025 millimeters of vanillin.

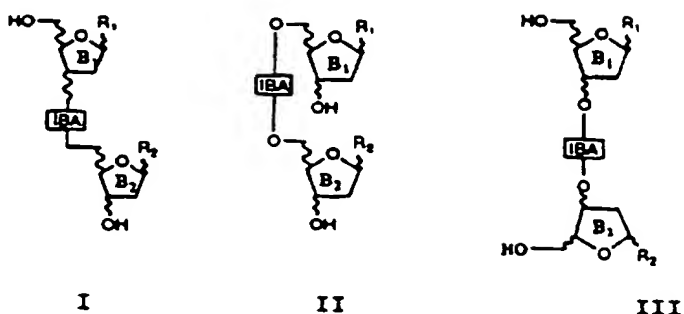
 The dimers prepared for the studies described herein are shown in Figures 1 and 6. Specific combinations of the dimers are shown in Table 1.

Table 1 - Structures of the Dinucleoside Monophosphate Dimers

Compound #	A	B
1	β -L-5FUdR	β -D-5UdR
2	β -L-5FUdR	α -L-5UdR
3	β -L-5FUdR	β -L-5FUdR
4	α -L-5UdR	α -L-5UdR
5	β -D-5FUdR	β -L-5FUdR
6	α -L-5UdR	β -L-5FUdR
7	α -L-dU	β -D-5FUdR
8	α -L-dC	β -D-5FUdR
9	α -L-dT	β -D-5FUdR
10	β -L-dU	β -D-5FUdR
11	β -L-dC	β -D-5FUdR
12	β -L-dT	β -D-5FUdR
13	α -L-5UdR	β -L-5FUdR
14	β -D-5FUdR	α -L-dC
15	α -L-5FUdR	β -D-5FUdR (3'-3')
16	β -D-5FUdR	β -L-dU
17	α -L-5FUdR	β -L-5FUdR
18	α -L-dG	β -D-5FUdR
19	β -L-dG	β -D-5FUdR
20	β -L-dA	β -D-5FUdR
21	β -D-1-OMe.dR	β -L-5FUdR
22	β -L-1-OMe.dR	β -D-5FUdR

The synthesis schemes in Figures 2 to 6 show the general synthesis pathways for the dimers. Specific synthesis pathways are more fully discussed in the examples.

A compound of the formulae:



or a pharmaceutically acceptable salt thereof, wherein B₁ and B₂ are each selected from the group consisting of the β -D, β -L, and the α -L nucleosides and wherein at least one of B₁ or B₂ must be β -L or α -L nucleoside, R₁ and R₂ are selected from the group of bases consisting of cytosine (C), thymine (T), uracil (U), adenine (A), guanosine (G), inosine (I), 5-fluorouridine (5FUdR) and other 5-halo bases and wherein R₁ and R₂ can be the same or a different base and wherein when B₁ or B₂ is attached to the internucleotide binding agent (IBA) at the 5' position and said B₁ or B₂ is β -L or α -L then the R₁ or R₂ attached to said B₁ or B₂ cannot be cytosine, and IBA is selected from the group consisting of phosphodiester, methoxy phosphotriesters, methylphosphonates and phosphorodithioates.

Specific compounds of the present invention which are effective include 3'-O-(α -L-5-fluoro-2'-deoxyuridinyl)- β -D-5-fluoro-2'-deoxyuridine, (L-102), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)- α -L-5-fluoro-2'-deoxyuridine, (L-103), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)- α -L-2'-deoxyuridine, (L-107), 3'-O-(α -L-5-fluoro-2'-deoxyuridinyl)- α -L-5-fluoro-2'-deoxyuridine, (L-108), 3'-O-(β -L-5-fluoro-2'-deoxyuridinyl)- β -L-5-fluoro-2'-deoxyuridine, (L-109), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)- β -L-5-fluoro-2'-deoxyuridine, (L-110), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)- α -L-2'-deoxycytidine, (L-111), 3'-O-(β -

D-5-fluoro-2'-deoxyuridiny1)-2'-deoxy- β -L-cytidine (L-113), 3'-O-(2'-deoxy- β -L-cytidiny1)- β -D-5-fluoro-2'-deoxyuridine (L-114), 3'-O-(2'-deoxy- α -L-cytidiny1)- β -D-5-fluoro-2'-deoxyuridine (L-115), 3'-O-(β -D-5-fluoro-2'-deoxyuridiny1)- β -L-2'-deoxyuridine (L-117), 3'-O-(β -L-5-fluoro-2'-deoxyuridiny1)- α -L-5-fluoro-2'-deoxyuridine (L-119), 3'-O-(β -D-5-fluoro-2'-deoxyuridiny1)- α -L-5-fluoro-2'-deoxyuridine (3', 3') (L-122).

More specifically, L-103, L-110 and L-117 are found to be the preferred compounds.

Another embodiment of the present invention is a pharmaceutical composition comprised of a pharmaceutically acceptable carrier and, a therapeutically effective amount of at least one compound of the present invention.

A further embodiment of the present invention is the administration of a therapeutically effective amount of the compounds of the present invention for the treatment of cancer or viral infections.

The following examples are offered by way of illustration and are not intended to limit the invention in any manner. The synthetic nucleosides and dimers described in the examples can include any of the substitutions discussed earlier. The backbone and base modifying groups can be added. The substitutions will enhance its affinity, the chemical stability and the cellular uptake properties of the specific dimers treatments.

Example 1

Synthesis of 2'-deoxy- α -L-5-fluorouridine

While β -D-5-fluoro-deoxyuridine is commercially available, the α -L-isomer 2'-deoxy- α -L-5-flourouridine is not, and this component of the dimers was synthesized from L-arabinose.

1-(2', 3', 5'-Tri-O-benzoyl- α -L-arabinofuranosyl)-5-fluorouracil (3)

To a mixture of 5-fluorouracil (4.01 g, 30.87 mmol) and compound 2 (15.57 g, 30.87 mmol) in anhydrous MeCN were successively added HMDS (5.20 ml, 24.69 mmol), ClSiMe_3 (3.10 ml, 24.69 mmol), and SnCl_4 (4.30 ml, 37.04 mmol). The resulting clear solution was refluxed for one hour. Then the solvent was evaporated and the residue was dissolved in EtOAc (750 ml), washed with H_2O , and saturated NaHCO_3 solution. The EtOAc layer was dried over sodium sulfate, filtered and evaporated to give the crude product. This crude product was purified on a silica gel column using 40-50% EtOAc/petroleum ether to give pure 3 (11.7 g, 66.0% yield) as a white foam.

NMR : (CDCl_3) δ = 4.65 (dd, 1H), 4.78 (dd, 1H), 4.97 (dd, 1H), 5.75-5.88 (2 t, 2H), 6.27 (d, 1H), 7.36-7.62 and 8.00-8.10 (m, 5H), 8.94 (d, 1H).

1- α -L-Arabinofuranosyl-5-fluorouracil (4)

To a solution of compound 3 (11.7 g, 20.37 mmol) in MeOH (300 ml), NaOMe (4.2 ml of a methanolic 25% w/v solution) was added and the solution was stirred until the reaction was complete. The solvent was then evaporated and the residue was dissolved in H_2O (200 ml), washed with ether and neutralized with Dowex 50 ion exchange resin. After filtration of the resin, the aqueous solution was evaporated to give compound 4 (4.92 g, 92% yield) as a white foam.

NMR : ($\text{DMSO}-d_6$) δ = 3.48 (m, 2H), 3.93-4.00 (2 t, 2H), 4.16 (q, 1H), 5.69 (dd, 1H), 8.03 (d, 1H).

1-[3', 5'-O-(1,1,3,3-tetraisopropylidisiloxane-1,3-diyl)- α -L-Arabinofuranosyl]-5-fluorouracil (5)

To a stirred suspension of 4 (6.43 g, 24.52 mmol) in pyridine (200 ml) was added 1,3-dichloro-1,1,3,3-tetraisopropylidisiloxane (10.3 ml, 29.43 mmol). This was stirred at room temperature until the reaction was complete (5 hours). The solvent was evaporated to a

residue which was dissolved in EtOAc and washed successively with H₂O, 5% HCl, H₂O, saturated NaHCO₃, and brine. After drying the EtOAc portion over Na₂SO₄, the solution was filtered and evaporated to give the crude product 5 which was used in the next step without further purification.

1-[2'-O-phenoxycarbonyl-3',5'-O-(1,1,3,3-tetraisopropylidisiloxane-1,3-diyl)-α-L-arabinofuranosyl]-5-fluorouracil (6)

To a solution of 5 (24.52 mmol) in anhydrous MeCN (300 ml) were added 4-dimethylaminopyridine (DMAP) (5.80 g, 47.58 mmol), and phenylchlorothionoformate (3.85 ml, 26.98 mmol). The solution was stirred at room temperature for 24 hours. Then, the solvent was evaporated to a residue which was dissolved in EtOAc and washed successively with H₂O, 5% HCl, H₂O, saturated NaHCO₃, and brine. After drying the EtOAc portion over Na₂SO₄, the solution was filtered and evaporated to an oil. The oil was purified on a silica gel column using 30% EtOAc/petroleum ether to produce pure 6 (8.9 g, 56.7% yield) as a yellow foam.

NMR: (CDCl₃) δ = 4.02 (m, 2H), 4.32 (m, 1H), 4.76 (dd, 1H), 6.10 (dd, 1H), 6.18 (dd, 1H), 7.0'-7.48 (m, 6H), 8.41 (br s, 1H).

3',5'-O-(1,1,3,3-Tetraisopropylidisiloxane-1,3-diyl)-α-L-2'-deoxy-5-fluorouridine (7)

To a solution of 6 (8.92 g, 13.91 mmol), in dry toluene (300 ml) was added AIBN (0.46 g, 2.78 mmol) followed by Bu₃SnH (20.0 ml, 69.35 mmol). The solution was deoxygenated with argon and heated at 75°C for four hours. The solvent was then evaporated and the residue was purified on a silica gel column using 30% EtOAc/petroleum ether to give pure 7 (5.44 g, 80% yield) as a white foam.

NMR: (CDCl₃) δ = 2.16 (m, 1H), 2.84 (m, 1H), 3.78 (m, 1H), 4.07 (m, 1H), 4.60 (m, 1H), 6.19 (ddd, 1H), 7.92 (m, 1H).

2'-Deoxy- α -L-5-fluorouridine (8)

A solution of compound 7 (5.44 g, 11.13 mmol) and NH_4F (4.12 g, 111.3 mmol) in MeOH was stirred in an oil bath at 60°C for 5 hours. Silica gel (3 g) was added and the mixture was evaporated to a dry powder. This powder was added to a silica column and eluted with 10-15% MeOH/ CHCl_3 to produce pure 8 (2.4 g, 87.6% yield) as a white foam.

NMR: ($\text{DMSO}-d_6$) δ = 1.90 (m, 1H), 2.55 (m, 1H), 3.33 (m, 2H), 4.19 (m, 2H), 4.86 (br s, 1H), 5.43 (br s, 1H), 6.10 (dd, 1H), 8.15 (d, 1H), 11.78 (br s, 1H).

Example 2Synthesis of 2'-deoxy- α -L-uridine1-(2', 3', 5'-Tri-O-benzoyl- α -L-arabinofuranosyl)uracil (9)

To a mixture of uracil (7.06g, 62.98 mmol) and compound 2 (31.7 g, 62.98 mmol) in anhydrous MeCN were successively added HMDS (10.6 ml, 50.38 mmol), ClSiMe_3 (6.4 ml, 50.38 mmol), and SnCl_4 (8.8 ml, 75.57 mmol). The resulting clear solution was refluxed for one hour. Then the solvent was evaporated and the residue was dissolved in EtOAc (1.21 ml), washed with H_2O , and saturated NaHCO_3 solution. The EtOAc layer was dried over Na_2SO_4 , filtered and evaporated to give the crude product. This crude product was purified on a silica gel column 50% using EtOAc/petroleum ether to give pure 2 (20.2 g, 57.7% yield) as a white foam.

NMR: (CDCl_3) δ = 4.65 (m, 2H), 4.95 (m, 1H), 5.79 (dd, 1H), 5.94 (t, 1H), 6.20 (d, 1H), 7.35-7.63 (m, 10H), 7.98-8.10 (m, 6H), 8.58 (br s, 1H).

1- α -L-Arabinofuranosyl-uracil (10)

To a solution of compound 8 (17.83 g, 32.03 mmol) in MeOH (400 ml), NaOMe (5.0 ml of a methanolic 25% w/v solution) was added and the solution was stirred until the reaction was complete. The solvent was then evaporated and the residue was dissolved in H_2O (250

ml), washed with ether and neutralized with Dowex 50 ion exchange resin. After filtration of the resin, the aqueous solution was evaporated to give compound 10 (7.4 g, 94.6% yield) as a white foam. This was used in the next step without further purification.

1-[3',5'-O-(1,1,3,3-Tetraisopropylidisiloxane-1,3-diyl)- α -L-arabinofuranosyl]-uracil (11)

To a stirred suspension of 10 (7.4 g, 30.3 mmol) in pyridine was added 1,3-dichloro-1,1,3,3-tetraisopropylidisiloxane (12.74 ml, 36.36 mmol). This was stirred at room temperature until the reaction was complete (5 hours). The solvent was evaporated to a residue which was dissolved in EtOAc (500 ml) and washed successively with H₂O, 5% HCl, H₂O, saturated NaHCO₃, and brine. After drying the EtOAc portion over Na₂SO₄, the solution was filtered and evaporated to give the crude product 11 which was used in the next step without further purification.

1-[2'-O-Phenoxythiocarbonyl-3',5'-O-(1,1,3,3-tetraisopropylidisiloxane-1,3-diyl)- α -L-arabinofuranosyl]-uracil (12)

To a solution of 11 (30.3 mmol) in anhydrous MeCN were added 4-dimethylaminopyridine (DMAP) (7.2 g, 58.78 mmol), and phenylchlorothionoformate (4.7 ml, 33.33 mmol). The solution was stirred at room temperature for 24 hours. Then, the solvent was evaporated to a residue which was dissolved in EtOAc (750 ml) and washed successively with H₂O, 5% HCl, H₂O, saturated NaHCO₃, and brine. After drying the EtOAc portion over Na₂SO₄, the solution was filtered and evaporated to an oil. The oil was purified on a silica gel column using 30% EtOAc/petroleum ether to produce pure 12 (13.14 g, 74.5% yield) as a white foam.

NMR: (CDCl₃) δ = 4.04 (m, 2H), 4.38 (m, 1H), 4.73 (dd, 1H), 5.79 (dd, 1H), 5.93 (d, 1H), 6.31 (dd, 1H), 7.08-7.33 (m, 6H), 9.2 (br s, 1H).

3',5'-O-(1,1,1,3-Tetraisopropylidisiloxane-1,3-diyl)- α -L-2'-deoxyuridine (13)

To a mixture of 12 (13.14 g, 21.09 mmol), in dry toluene (300 ml) was added AIBN (0.69 g, 4.2 mmol) followed by Bu_3SnH (28.4 ml, 105.4 mmol). The solution was deoxygenated with argon and heated at 75°C for four hours. The solvent was then evaporated and the residue was purified on a silica gel column using 30% EtOAc/petroleum ether to give pure 13 (9.29 g, 88.4% yield) as a white foam.

NMR: (CDCl_3) δ = 2.15 (2 t, 1H), 2.81 (m, 1H), 3.82 (dd, 1H), 4.05 (m, 2H), 4.56 (q, 1H), 5.75 (dd, 1H), 6.15 (t, 1H), 7.69 (d, 1H), 9.38 (br s, 1H).

2'-Deoxy- α -L-uridine (14)

A mixture of compound 13 (9.2 g, 18.63 mmol) and NH_4F (6.9 g, 186.3 mmol) in MeOH (200 ml) was stirred in an oil bath at 60°C for 3 hours. Silica gel (5 g.) was added and the mixture was evaporated to a dry powder. This powder was added to a silica column and eluted with 10-15% MeOH/ CHCl_3 to produce pure 14 (3.70 g, 83% yield) as a white foam.

NMR: ($\text{DMSO}-d_6$) δ = 1.87 (m, 1H), 2.56 (m, 1H), 3.41 (m, 2H), 4.15 (m, 1H), 4.22 (m, 1H), 4.44 (t, 1H), 4.92 (t, 1H), 5.38 (d, 1H), 5.62 (d, 1H), 6.09 (dd, 1H).

Example 3

Synthesis of 2'-deoxy- α -L-cytidine

1',5'-Di-O-benzoyl-2'-deoxy- α -L-uridine (15)

A solution of BzCN (0.61 g, 4.67 mmol) in MeCN (10 ml) was added dropwise to a suspension of compound 14 (0.43 g, 1.87 mmol) in MeCN (10 ml) followed by Et_3N (0.1 ml). The reaction was stirred at room temperature for three hours after which time the solvent was evaporated to dryness. The crude material was purified on a silica gel column using 50% EtOAc/petroleum ether to give pure 15 (0.57 g, 70% yield) as yellow foam.

NMR: (CDCl₃) δ = 2.55 (d, 1H), 2.96 (dt, 1H), 4.56 (m, 2H), 4.86 (t, 1H), 5.61 (d, 1H), 5.72 (dd, 1H), 6.31 (dd, 1H), 7.40-7.63 (m, 7H), 7.87-8.06 (m, 4H), 8.82 (br s, 1H).

5 3',5'-Di-O-benzoyl-2'-deoxy-4-thio- α -L-uridine (16)

A boiling solution of compound 15 (0.54 g, 1.25 mmol) in anhydrous dioxane was treated with P₂S₅ (0.61 g, 2.75 mmol) and the mixture was refluxed under a nitrogen atmosphere for one hour. Remaining solids were filtered from the hot solution and washed on the filter with additional dioxane. The filtrate was evaporated to dryness and the crude product was purified on a silica gel column using 30% EtOAc/petroleum ether to give pure 16 (0.42 g, 74% yield) as a yellow oil.

NMR: (CDCl₃) δ = 2.59 (d, 1H), 2.93 (dt, 1H), 4.58 (m, 2H), 4.89 (t, 1H), 5.63 (d, 1H), 6.26 (dd, 1H), 6.41 (dd, 1H), 7.40-8.10 (m, 11H), 9.54 (br s, 1H).

20 2'-Deoxy- α -L-cytidine (17)

Compound 16 (0.42 g, 9.28 mmol) was treated with NH₃/MeOH (50 ml) in a steel bomb at 100°C for 10 hours. After cooling, the solvent was evaporated to dryness, the residue was dissolved in water (50 ml) and washed with ether (3 x 50 ml). The water layer was treated with charcoal, filtered through Celite and evaporated to dryness by coevaporation with EtOH. The semi-solid obtained was crystallized from EtOH/ether to give compound 17 (0.18 g, 85.7% yield).

30 NMR: (DMSO-d₆) δ = 1.66 (d, 1H), 2.50 (m, 1H), 3.40 (m, 1H), 4.12 (m, 1H), 4.15 (m, 1H), 4.86 (t, 1H), 5.21 (d, 1H), 5.69 (d, 1H), 6.03 (dd, 1H), 7.02 (br d, 1H), 7.74 (d, 1H).

N⁴-benzoyl-2'-deoxy- α -L-cytidine (18)

35 To a stirring suspension of compound 17 (0.82 g, 3.61 mmol) in pyridine (50 ml) chilled in an ice bath ClSiMe₃ (2.3 ml, 18.05 mmol) was added dropwise over 30 minutes. SzCl (2.1 ml, 18.05 mmol) was then added

dropwise and the reaction mixture was cooled at room temperature for two hours. The reaction mixture was again cooled in an ice bath and cold water (10 ml) was added dropwise. Fifteen minutes later, concentrated
5 NH_4OH (10 ml) was added to produce a solution ammonia concentration of about 2M. Thirty minutes after the addition of the ammonia solution, the solvent was evaporated, dissolved in water and washed with ether. Evaporation of this aqueous solution provided the crude
10 product (18) which was used in the next step without further purification.

N^4 -Benzoyl-5'-O-(di-p-methoxytrityl)-2'- α -L-cytidine
(19)

To a solution of compound 18 in dry pyridine was
15 added 4,4'-dimethoxytrityl chloride (1.34 g, 3.96 mmol), DMF-P (0.888 g, 0.72 mmol), and triethylamine (0.8 ml, 5.54 mmol). The reaction mixture was stirred at room temperature overnight. The EtOAc solution was washed with water, saturated NaHCO_3 , and brine. The
20 solution was then dried over Na_2SO_4 , filtered and evaporated to dryness. The crude material was purified on a silica gel column using 5% $\text{MeOH}/\text{CHCl}_3$ to produce pure 19 (1.08 g, 47% yield). Some of the starting material, 18, was recovered and recycled.

25 NMR: (CDCl_3 , δ = 2.60 (d, 1H), 2.82 (m, 1H), 3.18 (dd, 1H), 3.30 (dd, 1H), 3.80 (s, 1H), 4.50 (d, 1H), 4.55 (t, 1H), 6.18 (d, 1H), 6.82 (d, 4H), 7.20-7.65 (m, 14), 7.90 (d, 1H), 8.12 (d, 1H). R_f = 0.46 in 10% $\text{MeOH}/\text{CHCl}_3$.

30 This compound was then redissolved in pyridine (10 ml). Acetic anhydride (2 ml) was added and the mixture was stirred at room temperature for 3.5 hours. The pyridine was removed in vacuo and the residue was partitioned between EtOAc and 0.1 N HCl. Then the
35 organic layer was washed successively with saturated NaHCO_3 and brine. The EtOAc solution was dried over Na_2SO_4 and evaporated to a colorless foam (754 mg).

NMR: (DMSO- d_6 , δ = 1.95 (s, 3H), 2.36 (m, 1H), 3.75-3.85 (m, 2H), 4.09 (m, 1H), 4.45 (m, 1H), 6.26 (t, 1H), 8.05 (d, 1H).

Example 4

Synthesis of Dimers

The dimers were prepared from the monomeric materials by the general scheme shown in Scheme 2.

A. α -L, β -D 5' FUDP Dimer (L-103)

5'-O-Dimethoxytrityl- α -L-5-fluoro-2'-deoxyuridine (20a)

10 α -L-5-fluoro-2'-deoxyuridine (19a) was dissolved in 10 ml of dry, distilled pyridine. To this solution was added 4,4'-dimethoxytrityl chloride (813 mg, 2.4 mmol) and 4-dimethylaminopyridine (DMAP) (50 mg, 0.4 mmol). The mixture was stirred under an argon
15 atmosphere for 16 hours. After this time, the pyridine was stripped off in vacuo. The residue was dissolved in dichloromethane (50 ml). The organic layer was washed with 0.3N HCl, brine, saturated NaHCO₃, water and again with brine. The organic layer was dried over
20 Na₂SO₄, filtered and evaporated in vacuo to a residue which was purified on a silica gel column using 10% MeOH/CHCl₃. Pure fractions were pooled and evaporated to give the pure product as an off-white foam (679 mg, 86% yield). Rf = 0.48 in 10% MeOH/CHCl₃.

25 NMR: (DMSO- d_6) δ = 2.3 (dd, 1H), 2.72-2.81 (m, 1H), 3.15-3.26 (m, 2H), 3.75 (s, 6H), 4.45 (m, 2H), 6.23 (dd, 1H), 6.92 (d, 1H), 7.2-7.3 (m, 13 H), 7.94 (d, 1H).

5'-O-Dimethoxytrityl- α -L-5-fluoro-2'-deoxyuridine-3'-

N,N-diisopropylmethoxy phosphoramidite (21a)

30 The 5'-O-dimethoxytrityl- α -L-5-fluoro-2'-deoxyuridine (20a, 548 mg, 1 mmol) was dissolved in anhydrous dichloromethane (20 ml). N,N-diisopropylethylamine (518 mg, 700, μ l) was added
35 through a septum, followed by chloro-N,N-

diisopropylmethoxyphosphine (297 mg), under an argon atmosphere. The reaction was stirred for 30 minutes. The solvent was evaporated and the residue was partitioned between an 80% EtOAc/triethylamine mixture and brine. The organic layer was washed with 0.1 N HCl, saturated NaHCO₃ solution and brine. The organic residue was evaporated to dryness and the residue was purified on a silica gel column using a mixture of dichloromethane, EtOAc and triethylamine (45:45:10; Rf = 0.69). The product (390 mg) was isolated as a yellow foam and it was used in the next step without further purification.

3'-O-Acetoxy 5'-dimethoxytrityl β -D-5-fluoro-2'-deoxyuridine (22b)

β -D-5-fluoro-2'-deoxyuridine (22b, 492 mg, 2 mmol) was dissolved in 10 ml of dry, distilled pyridine. To this solution was added 4,4'-dimethoxytrityl chloride (813 mg, 2.4 mmol) and DMAP (50 mg, 0.4 mmol). The mixture was stirred under an argon atmosphere for 16 hours. After this time, the pyridine was stripped off in vacuo. The residue was dissolved in dichloromethane (50 ml). The organic layer was washed with 0.3 N HCl, brine, saturated NaHCO₃, and brine. The organic layer was dried over Na₂SO₄, filtered and evaporated in vacuo to a residue which was purified on a silica gel column, using 10% MeOH/CHCl₃. Pure fractions were pooled and evaporated to give the pure product as an off-white foam (694 mg, 88% yield). Rf = 0.46 in 10% MeOH/CHCl₃.

This compound was then redissolved in pyridine (10 ml). Acetic anhydride (2 ml) was added and the mixture was stirred at room temperature for 3.5 hours. The pyridine was removed in vacuo and the residue was partitioned between EtOAc and 0.1 N HCl. Then the organic layer was washed successively with saturated NaHCO₃ and brine. The EtOAc solution was dried over Na₂SO₄ and evaporated to a colorless foam (754 mg).

NMR: (DMSO- d_6) δ = 1.95 (s, 3H), 2.36 (m, 1H), 3.75-3.85 (m, 2H), 4.08 (m, 1H), 4.45 (m, 1H), 6.26 (t, 1H), 8.05 (d, 1H).

5 5'-O-Dimethoxytrityl-3'-(O-(2'-O-acetyl))- β -D-5-fluoro-2'-deoxyuridinyl)- α -L-5-fluoro-2'-deoxyuridine methyl phosphite ester (23a)

The 3'-acetyl- β -D-5-fluoro-2'-deoxyuridine (355 mg, 0.62 mmol) was dissolved in dry acetonitrile (5 ml). Sublimed 1H-tetrazole (80 mg) was added and the mixture was stirred under an argon atmosphere for 15 minutes. The solution of 21a (390 mg, 0.6 mmol), dissolved in 5 ml of dry acetonitrile was added via syringe to the reaction solution over 5 minutes. The mixture was allowed to stir at room temperature for three hours. The acetonitrile was evaporated in vacuo to a residue. This residue was triturated with a 70% EtOAc/ether mixture. The undissolved tetrazole was filtered off and the filtrate was evaporated to give a dry yellow foam (468 mg). This foam was used in the next step without further purification.

20 (3'-Acetoxy- β -D-5-fluoro-2'-deoxyuridinyl)- α -L-5-fluoro-2'-deoxyuridine methyl phosphat- ester (26a)

The dimer, 25a (504 mg), was dissolved in 8 ml of THF and 2 ml of 2,6 lutidine containing 0.2 ml of water. Iodine crystals (26 mg) were added and the contents of the loosely stoppered flask were allowed to stir for 2.5 hours. Excess iodine was discharged by the addition of one or two drops of saturated sodium thiosulfate. The reaction mixture was then evaporated to dryness. The residue (530 mg) was dissolved in 10 ml of 80% acetic acid/water solution and was stirred for three hours. The solvent was evaporated and the residue was purified on a silica gel column, using 20% MeOH/ $CHCl_3$. Fractions containing one spot by TLC (10% MeOH/ $CHCl_3$, R_f =0.35) were pooled and evaporated to give the pure product (316 mg).

NMR: (DMSO- d_6) δ = 1.96 (s, 3H), 2.2-2.4 (m, 2H), 2.65-2.72 (m, 1H), 3.54-3.85 (m, 4H), 4.02 (m, 1H), 4.45 (m, 2H), 6.08 (dd, 1H), 6.26 (dt, 1H), 8.05 (d, 1H), 8.08 (d, 1H).

5 **P^1 NMR:** (CD $_3$ OD) δ = 0.77 (s), 1.16 (s).

3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)- α -L-5-fluoro-2'-deoxyuridine (27a) [α -L, β -D-5-FuDR Dimer-3'-5'-103]

10 The O-protected dimer, 26a (280 mg) was treated with 20 ml of saturated methanolic ammonia for 16 hours at room temperature. The solvent was stripped of in vacuo and the residue was triturated with chloroform (3 X 20 ml). The triturate was decanted off and the residue was purified by silica gel chromatography, using 30% MeOH/CHCl $_3$. Pure fractions were evaporated to dryness to give the pure product (162 mg).

NMR: (D $_2$ O) δ = 2.2-2.4 (m, 2H), 2.65-2.71 (m, 1H), 3.54-3.85 (m, 5H), 4.05 (t, 1H), 4.42 (m, 2H), 6.06 (dd, 1H), 6.24 (dt, 1H), 8.04 (d, 1H), 8.06 (d, 1H).

P^1 NMR: (CD $_3$ OD) δ = 0.04 (s).

20 5'-O-Dimethoxytrityl- β -D-5-fluoro-2'-deoxyuridine-3'-N,N-diisopropylmethoxy phosphoramidite (21b)

25 The 5'-O-dimethoxytrityl- β -D-5-fluoro-2'-deoxyuridine (20a, 548 mg, 1 mmol) was dissolved in anhydrous dichloromethane (20 ml), N,N-diisopropylethylamine (518 mg, 700 ml) was added through a septum, followed by chloro-N,N-diisopropylmethoxyphosphine (297 mg), under an argon atmosphere. The reaction was stirred for 30 minutes. The solvent was evaporated and the residue was partitioned between an 80% EtOAc/triethylamine mixture and brine. The organic layer was washed with 0.1 N HCl, saturated NaHCO $_3$ solution and brine. The organic residue was evaporated to dryness and the residue was purified on a silica gel column using a mixture of dichloromethane, EtOAc and triethylamine (45:45:10; Rf=0.62). The product (431 mg) was isolated as a

yellow foam and it was used in the next step without further purification.

B. β -D, α -L 5FUdR Dimer

5 5'-O-Dimethoxytrityl-3'-(O-(3'-O-acetyl)- α -L-5-fluoro-2'-deoxyuridinyl)- β -D-5-fluoro-2'-deoxyuridine methyl phosphate ester (25b)

The 3'-O-acetyl- α -L-5-fluoro-2'-deoxyuridine, 24 (355 mg, 0.62 mmol) was dissolved in dry acetonitrile (5 ml). Sublimed 1H-tetrazole (80 mg) was added and the mixture was stirred under an argon atmosphere for 15 minutes. The solution of 21 (380 mg, 0.6 mmol), dissolved in 5 ml of dry acetonitrile was added via syringe to the reaction solution over 5 minutes. The mixture was allowed to stir at room temperature for three hours. The acetonitrile was evaporated in vacuo to a residue. This residue was triturated with a 70% EtOAc/ether mixture. The undissolved tetrazole was filtered off and the filtrate was evaporated to give a dry yellow foam (484 mg). This foam was used in the next step without further purification.

20 (3'-Acetoxy- α -L-5-fluoro-2'-deoxyuridinyl)- β -D-5-fluoro-2'-deoxyuridine methyl phosphate ester (26b)

The dimer in reduced form, 25b (526 mg), was dissolved in 8 ml of THF and 2 ml of 2.6 lutidine containing 0.2 ml of water. Iodine crystals (26 mg) were added and the contents of the loosely stoppered flask were allowed to stir for 2.5 hours. Excess iodine was discharged by the addition of one or two drops of saturated sodium thiosulfate. The reaction mixture was then evaporated to dryness. The residue (578 mg) was dissolved in 10 ml of 80% acetic acid/water solution and was stirred for three hours. The solvent was evaporated and the residue was purified on a silica gel column, using 20% MeOH/CHCl₃. Fractions containing one spot by TLC (10% MeOH/CHCl₃, R_f - 0.35) were pooled and evaporated to give the pure product (342 mg).

NMR: (DMSO- d_6) δ = 1.96 (s, 3H), 2.2-2.4 (m, 2H), 2.62-2.71 (m, 1H), 3.5-3.9 (m, 4H), 4.02 (m, 1H), 4.42 (m, 2H), 6.10 (dd, 1H), 6.26 (dt, 1H), 8.00 (d, 1H), 8.04 (d, 1H).

5 3'-O-(α -L-5-fluoro-2'-deoxyuridinyl)-3'-5')- β -D-5-fluoro-2'-deoxyuridine (β -D, α -L 5FUDR Dimer), L-102 (27b)

The O-protected dimer, 26b (170 mg) was treated with 20 ml of saturated methanolic ammonia for 16 hours at room temperature. The solvent was stripped off in vacuo and the residue was triturated with chloroform (3 X 20 ml). The triturate was decanted off and the residue was purified by silica gel chromatography, using 30% MeOH/CHCl₃. Pure fractions were evaporated to dryness to give the pure product (89 mg).

NMR: (D₂O) δ = 2.2-2.4 (m, 2H), 2.65-2.71 (m, 1H), 3.54-3.85 (m, 5H), 4.05 (t, 1H), 4.42 (m, 2H), 6.06 (dd, 1H), 6.23 (dt, 1H), 8.00 (d, 1H), 8.04 (d, 1H).

20 C. α -L 4U, β -D 5 FUDR dimer (L-107)
5'-O-(dimethoxytrityl)-2'-deoxy- α -L-uridine (20c)

α -L-2'-deoxyuridine (1.5 g, 6.57 mmol) was dissolved in 25 ml of dry, distilled pyridine. To this solution was added 4,4'-dimethoxytrityl chloride (2.9 g, 7.89 mmol) and 4-dimethylamino pyridine (DMAP) (160 mg, 1.31 mmol). The mixture was stirred under an argon atmosphere for 16 hours. After this time, the pyridine was stripped off in vacuo. The residue was dissolved in dichloromethane (50 ml). The organic layer was washed with 0.3 N HCl, brine, saturated NaHCO₃, and again with brine. The organic layer was dried over Na₂SO₄, filtered and evaporated in vacuo to a residue which was purified on a silica gel column using 5% MeOH/CHCl₃. Pure fractions were pooled and evaporated to give the pure product as an off-white foam (2.84 g, 81% yield).

NMR: (DMSO- d_6) δ = 2.29 (d, 1H), 2.70 (m, 2H), 3.17 (m, 2H), 3.78 (s, 6H), 4.44 (m, 2H), 5.63 (d, 1H), 6.19 (d, 1H), 6.83 (d, 4H), 7.28 (m, 9 H), 7.68 (d, 1H), 9.30 (br s, 1H).

5 5'-O-(dimethoxytrityl)- α -L-2'-deoxyuridine-3'-N,N-diisopropylmethoxy phosphoramidite (21c)

The 5'-O-dimethoxytrityl- α -L-2'-deoxyuridine (2.35 g, 4.43 mmol) was dissolved in anhydrous dichloromethane (50 ml). N,N-diisopropylethylamine (3.1 ml, 17.72 mmol) was added through a septum, followed by chloro-N,N-diisopropylmethoxyphosphine (1.3 ml, 6.64 mmol), under an argon atmosphere. The reaction was stirred for 30 minutes. The solvent was evaporated and the residue was partitioned between an 80% EtOAc/triethylamine mixture and brine. The organic layer was washed with .01 N HCl, saturated NaHCO₃ solution and brine. The organic residue was evaporated to dryness and the residue was purified on a silica gel column using a mixture of dichloromethane, EtOAc and triethylamine (40:50:10; R_f = 0.69). The product was isolated quantitatively as a yellow foam and it was used in the next step without further purification.

10 3'-Acetoxy-5'-O-dimethoxytrityl-3'-(O-5- β -D-fluoro-2'-deoxyuridinyl)-2'-deoxy- α -L-uridine methyl phosphite ester (23c)

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The 3'-O-acet, -D-5-fluoro-2'-deoxyuridine (0.95 g, 3.29 mmol) was dissolved in dry acetonitrile (125 ml). Sublimed 1H-tetrazole (350 mg, 4.91) was added and the mixture was stirred under an argon atmosphere for 15 minutes. The solution of 21c (4.91 mmol), dissolved in 5 ml of dry acetonitrile was added via syringe to the reaction solution over 5 minutes. The mixture was allowed to stir at room temperature for three hours. The acetonitrile was reduced in vacuo to a residue. This residue was triturated with a 70% EtOAc/ether mixture. The undissolved tetrazole was filtered off and the filtrate was evaporated to give a

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dry yellow foam. This compound was further purified on a silica gel column using 5% MeOH/CHCl₃ to give the pure product (2.81 g, 97% yield).

5 3'-acetoxy-β-D-5'-fluoro-2'-deoxyuridinyl)-α-L-2'-deoxyuridine methyl phosphate ester (26c)

The dimer in reduced form, 25c (2.81 g, 5.3 mmol), was dissolved in a mixture of THF:lutidine:water (25:6:0.6). Iodine crystals (150 mg) were added and the contents of the loosely stoppered flask were allowed to stir for 2.5 hours. Excess iodine was discharged by the addition of a few drops of saturated sodium thiosulfate. The reaction mixture was then evaporated to dryness. The residue (1.48 g) was dissolved in 25 ml of 80% acetic acid/water solution and was stirred for 3 hours. The solvent was evaporated and the residue was purified on a silica gel column, using 10% MeOH/CHCl₃. Fractions containing one spot by TLC (10% MeOH/CHCl₃, R_f = 0.35) were pooled and evaporated to give the pure product (0.465 g, 25% yield).

20 ¹H NMR: (CD₃OD) δ = 2.09 (d, 3H), 2.40 (m, 3H), 2.80 (m, 1H), 3.78 (dd, 3H), 4.30 (m, 3H), 4.63 (m, 1H), 5.05 (m, 1H), 5.23 (m, 1H), 5.70 (d, 1H), 6.13 (m, 1H), 6.20 (m, 1H), 7.73 (d, 1H), 7.82 (d, 1H).

25 ³¹P NMR: (CD₃OD) δ = 0.56 (s), 0.84 (s).

3'-O-(β-D-5'-fluoro-2'-deoxyuridinyl)(3'-5')-α-L-2'-deoxyuridine (L-1071) (27c)

The O-protected dimer, 26c (465 mg, 0.78 mmol) was treated with 50 ml of saturated methanolic ammonia at room temperature. The solvent was stripped off in vacuo and the residue was triturated with chloroform (3 X 20 ml). The triturate was decanted off and the residue was purified by silica gel chromatography, using 30% MeOH/CHCl₃. Pure fractions were evaporated to dryness to give the pure product (370 mg, 87.7% yield).

NMR: (CD₃OD) δ = 2.23 (m, 2H), 2.29 (d, 1H), 2.73 (m, 1H), 4.0 (d, 2H), 4.42 (m, 1H), 4.56 (m, 1H), 4.81 (m, 1H), 5.69 (d, 1H), 6.24 (m, 2H), 7.85 (d, 1H), 8.02 (d, 1H).

5 ³¹P-NMR: (CD₃OD) δ = 1.25 (s).

D. (L-109) β -L-5-L 5FUdR Dimer

5'-O-Dimethoxytrityl- β -L-5-fluoro-2'-deoxyuridine (203)

β -L-5-fluoro-2'-deoxyuridine (19d, 1.42 g, 5.77 mmol) was dissolved in 25 ml of dry, distilled
10 pyridine. To this solution was added 4,4'-dimethoxytrityl chloride (2.34 g, 6.92 mmol) and 4-dimethylamino pyridine (DMAP) (140 mg, 1.15 mmol). The mixture was stirred under an argon atmosphere for 16 hours. After this time, the pyridine was stripped off
15 in vacuo. The residue was dissolved in dichloromethane (50 ml). The organic layer was washed with 0.3 N HCl, brine, saturated NaHCO₃, and again with brine. The organic layer was dried over Na₂SO₄, filtered and evaporated in vacuo to a residue which was purified on
20 a silica gel column using 5% MeOH/CHCl₃. Pure fractions were pooled and evaporated to give the pure product as an off-white foam (2.88 g, 88.7% yield).
NMR: (CDCl₃) δ = 2.25 (m, 1H), 2.50 (m, 1H), 3.50 (m, 2H), 3.80 (s, 6H), 4.08 (m, 1H), 4.58 (m, 1H), 6.30 (t, 1H), 6.84 (d, 4H), 7.28 (m, 9 H), 7.82 (d, 1H), 8.58 (br s, 1H).

1'-O-Acetoxy-5'-O-dimethoxytrityl- β -D-5-fluoro-2'-deoxyuridine (234)

β -L-5-fluoro-2'-deoxyuridine (20d, 800 mg, 1.46 mmol) was dissolved in 30 ml of dry, distilled
30 pyridine. To this solution was added 4,4'-dimethoxytrityl chloride (813 mg, 2.4 mmol) and DMAP (40 mg, 0.29 mmol). The mixture was stirred under an argon atmosphere for 16 hours. After this time, the
35 pyridine was stripped off in vacuo. The residue was dissolved in dichloromethane (50 ml). The organic layer was washed with 0.3 N HCl, saturated NaHCO₃, and

brine. The organic layer was dried over Na_2SO_4 , filtered and evaporated in vacuo to a residue which was purified on a silica gel column using 10% $\text{MeOH}/\text{CHCl}_3$. Pure fractions were pooled and evaporated to give the pure product as an off-white foam (694 mg, 88% yield).
Rf = 0.46 in 10% $\text{MeOH}/\text{CHCl}_3$.

This compound was then redissolved in pyridine (10 ml). Acetic anhydride (2 ml) was added the mixture was stirred at room temperature for 3.5 hours. The pyridine was removed in vacuo and the residue was partitioned between EtOAc and 0.1 N HCl. Then the organic layer was washed successively with saturated NaHCO_3 and brine. The EtOAc solution was dried over Na_2SO_4 and evaporated to a colorless foam.

This foam was dissolved in 20 ml of 80% HOAc and stirred for three hours. The solvent was evaporated in vacuo and the residue was purified on a silica gel column using 10% $\text{MeOH}/\text{CHCl}_3$ to give (340 mg, 80% yield).

5'-O-Dimethoxytrityl- β -L-5-fluoro-2'-deoxyuridine-3'-N,N-diisopropylmethoxy phosphoramidite (21d)

The 5'-O-dimethoxytrityl- β -L-5-fluoro-2'-deoxyuridine (20d, 840 mg, 1.53 mmol) was dissolved in anhydrous dichloromethane (50 ml). N,N-diisopropylethylamine (1.1 ml, 6.13 mmol) was added through a septum, followed by chloro-N,N-diisopropylmethoxyphosphine (0.42 ml, 2.3 mmol), under an argon atmosphere. The reaction was stirred for 30 minutes. The solvent was evaporated and the residue was partitioned between an 80% EtOAc/triethylamine mixture and brine. The organic layer was washed with 0.1 N HCl, saturated NaHCO_3 solution and brine. The organic residue was evaporated to dryness and the residue was purified on a silica gel column using a mixture of dichloromethane, EtOAc and triethylamine (45:45:10; Rf = 0.69). The product (700 mg, 65%) was

isolated as a yellow foam and it was used in the next step without further purification.

5'-O-Dimethoxytrityl-3'-(O-(3'-O-acetyl)- β -L-5-fluoro-2'-deoxyuridinyl)- β -L-5-fluoro-2'-deoxyuridine methyl phosphite ester (25d)

5 The 3'-acetyl- β -L-5-fluoro-2'-deoxyuridine, 24d (330 mg, 1.15 mmol) was dissolved in dry acetonitrile (50 ml). Sublimed 1H-tetrazole (120 mg, 1.77 mmol) was added and the mixture was stirred under an argon atmosphere for 15 minutes. The solution of 21d (950 mg, 1.36 mmol), dissolved in 5 ml of dry acetonitrile was added via syringe to the reaction solution over 5 minutes. The mixture was allowed to stir at room temperature for three hours. The acetonitrile was reduced in vacuo to a residue. This residue was trituated with a 70% EtOAc/ether mixture. The undissolved tetrazole was filtered off and the filtrate was evaporated to give a dry yellow foam. This foam was purified on a silica gel column using 5% MeOH/CHCl₃, to give the pure product (960 mg, 93% yield).

20 NMR: (CDCl₃) δ = 2.10 (d, 3H), 2.28 (m, 2H), 2.49 (m, 2H), 3.42 (m, 3H), 3.51 (dd, 3H), 3.76 (s, 6H), 4.07 (m, 1H), 4.55 (m, 1H), 4.87 (m, 1H), 5.23 (m, 1H), 6.30 (m, 2H), 6.84 (d, 4H), 7.30 (m, 9H), 7.82 (m, 2H).

25 (3'-Acetoxy- β -D-5-fluoro-2'-deoxyuridinyl)- α -L-5-fluoro-2'-deoxyuridine methyl phosphate ester (26d)

The dimer in reduced form, 25d (960 mg, 1.07 mmol), was dissolved in a mixture containing THF:lutidine:water (12:3:0.3). Iodine crystals (50 mg) were added and the contents of the loosely stoppered flask were allowed to stir for 2.5 hours. Excess iodine was discharged by the addition of one or two drops of saturated sodium thiosulfate. The reaction mixture was then evaporated to dryness. The residue (530 mg) was dissolved in 20 ml of 80% acetic acid/water solution and was stirred for three hours. The solvent was evaporated and the residue was purified

on a silica gel column, using 10% MeOH/CHCl₃.

Fractions containing one spot by TLC (10% MeOH/CHCl₃, R_f = 0.35) were pooled and evaporated to give the pure product (310 mg, 46% yield).

5 ¹H NMR: (CD₃OD) δ = 2.08 (s, 3H), 2.35-2.54 (m, 4H), 3.79 (m, 2H), 3.83 (dd, 3H), 4.18 (m, 2H), 5.08 (m, 1H), 5.29 (m, 1H), 6.24 (m, 1H), 7.86 (dd, 1H), 8.19 (dd, 1H).

³¹P NMR: (CD₃OD) δ = 0.82 (s), 1.03 (s).

10 3'-O-(β-L-5-fluoro-2'-deoxyuridinyl)-(3'-5')-β-L-5-fluoro-2'-deoxy uridine (27d) [L-109]

The O-protected dimer, 26d (300 mg, 0.49 mmol) was treated with 50 ml of saturated methanolic ammonia for 16 hours at room temperature. The solvent was stripped off in vacuo and the residue was triturated with chloroform (3 X 20 ml). The triturate was decanted off and the residue was purified by silica gel chromatography, using 30% MeOH/CHCl₃. Pure fractions were evaporated to dryness to give the pure product (240 mg, 85% yield).

20 ¹H NMR: (CD₃OD) δ = 2.25 (m, 3H), 2.50 (m, 1H), 3.79 (d, 2H), 4.03 (m, 1H), 4.08 (m, 2H), 4.18 (m, 1H), 4.44 (m, 1H), 4.90 (m, 1H), 6.25 (t, 1H), 8.01 (d, 1H), 8.24 (d, 1H).

25 ³¹P NMR: (CD₃OD) δ = 0.18 (s).

B. β-L, β-D-5'UTdR Dimer L-110

5'-O-Dimethoxytrityl-3'-(O-(3'-O-acetyl)-β-L-5-fluoro-2'-deoxyuridinyl)-β-D-5-fluoro-2'-deoxyuridine methyl phosphite ester (25a)

30 The 3'-O-acetyl-β-D-5-fluoro-2'-deoxyuridine (250 mg, 0.97 mmol) was dissolved in dry acetonitrile (50 ml). Sublimed 1H-tetrazole (100 mg, 1.46 mmol) was added and the mixture was stirred under an argon atmosphere for 15 minutes. The solution of 21a (1.02 g, 1.46 mmol), dissolved in 5 ml of dry acetonitrile was added via syringe to the reaction solution over 5 minutes. The mixture was allowed to stir at room

temperature for three hours. The acetonitrile was reduced in vacuo to a residue. This residue was triturated with a 70% EtOAc/ether mixture. The undissolved tetrazole was filtered off and the filtrate was evaporated to give a dry yellow foam. This foam was purified on a silica gel column using 5% MeOH/CHCl₃ to give the pure product quantitatively.

(3'-Acetoxy-β-L-5-fluoro-2'-deoxyuridinyl)-β-D-5-fluoro-2'-deoxyuridine methyl phosphate ester (26e)

The dimer in reduced form, 25e (700 mg, 0.78 mmol), was dissolved in a mixture containing THF:lutidine:water (25:6:0.6). Iodine crystals (100 mg) were added and the contents of the loosely stoppered flask were allowed to stir for 2.5 hours. Excess iodine was discharged by the addition of one or two drops of saturated sodium thiosulfate. The reaction mixture was then evaporated to dryness. The residue was dissolved in 25 ml of 80% acetic acid/water solution and was stirred for three hours. The solvent was evaporated and the residue was purified on a silica gel column, using 10% MeOH/CHCl₃. Fractions containing one spot by TLC (10% MeOH/CHCl₃, R_f = 0.35) were pooled and evaporated to give the pure product (340 mg, 71.4% yield).

¹H NMR: (DMSO-d₆) δ = 2.06 (s, 3H), 2.37 (m, 4H), 3.45 (m, 2H), 3.65 (d, 3H), 4.20 (m, 3H), 4.95 (m, 1H), 5.30 (m, 1H), 5.96 (m, 1H), 6.15 (t, 2H), 7.99 (d, 1H), 8.16 (d, 1H), 11.90 (br s, 2H).

³¹P NMR: (DMSO-d₆) δ = 1.93 (s), 2.01 (s).

3'-O-(β-L-5-fluoro-2'-deoxyuridinyl)-(3'-5')-β-D-5-fluoro-2'-deoxyuridine (27e) (L-116)

The O-protected dimer, 26e (340 mg, 0.57 mmol) was treated with 100 ml of saturated methanolic ammonia for 16 hours at room temperature. The solvent was stripped off in vacuo and the residue was triturated with chloroform (3 X 20 ml). The triturate was decanted off and the residue was purified by silica gel

chromatography, using 30% MeOH/CHCl₃. Pure fractions were evaporated to dryness to give the pure product (200 mg, 66.9% yield).

5 NMR: (CD₃OD) δ = 2.20 (m, 3H), 2.53 (m, 1H), 3.79 (d, 2H), 4.05 (m, 3H), 4.16 (m, 1H), 4.45 (m, 1H), 6.27 (t, 2H), 8.01 (d, 1H), 8.04 (d, 1H), 8.26 (d, 1H).

7. α -L, β -D-5'NDR Dimer (3'-3') (L-122)

5'-O-(Dimethoxytrityl)- α -L-5-fluoro-2'-deoxyuridine-3'-N,N-diisopropylcyanoethyl phosphoramidite (21f)

10 The 5'-O-dimethoxytrityl- α -L-5-fluoro-2'-deoxyuridine (1.48 g, 2.71 mmol) was dissolved in anhydrous dichloromethane (50 ml). N,N-diisopropylethylamine (1.9 ml, 10.84 mmol) was added through a septum, followed by 2'-cyanoethyl-N,N-
15 diisopropylchlorophosphoramidite (0.78 ml, 3.52 mmol), under an argon atmosphere. The reaction was stirred for 30 minutes. The solvent was evaporated and the residue was partitioned between an 80% EtOAc/
20 triethylamine mixture and brine. The organic layer was washed with saturated NaHCO₃ solution and brine. The organic residue was evaporated to dryness and the residue was purified on a silica gel column using a mixture of dichloromethane, EtOAc and triethylamine
25 (45:45:10; Rf=0.7). The product was isolated quantitatively as a yellow foam and it was used in the next step without further purification.

5'-O-Dimethoxytrityl-3'-[O-(5'-O-dimethoxytrityl)- β -D-5-fluoro-2'-deoxyuridinyl]- α -L-5-fluoro-2'-deoxyuridine cyanoethyl phosphite ester (25f)

30 The 5'-O-dimethoxytrityl- β -D-5-fluoro-2'-deoxyuridine (0.44 g, 0.81 mmol) was dissolved in dry acetonitrile (20 ml). Sublimed 1H-tetrazole (90 mg) was added and the mixture was stirred under an argon atmosphere for 15 minutes. The solution of 21f
35 (0.51 mg, 0.67 mmol), dissolved in 10 ml of dry acetonitrile was added via syringe to the reaction solution over 5 minutes. The mixture was allowed to

stir at room temperature for three hours. The acetonitrile was evaporated in vacuo to a residue. This residue was triturated with a 70% EtOAc/ether mixture. The undissolved tetrazole was filtered off and the filtrate was evaporated to give a dry yellow foam (970 mg). This foam was used in the next step without further purification.

(β -D-5-fluoro-2'-deoxyuridinyl)- α -L-5-fluoro-2'-deoxyuridine cyanoethyl phosphate ester (26f)

10 The dimer, 25f (970 mg), was dissolved in 16 ml of THF and 4 ml of pyridine containing 0.4 ml of water. Iodine crystals (50 mg) were added and the contents of the loosely stoppered flask were allowed to stir for 1 hour. Excess iodine was discharged by the addition of
15 few drops of saturated sodium thiosulfate. The reaction mixture was then evaporated to dryness. The crude product was in EtOAc washed with saturated NaHCO₃ solution and brine. The organic layer was dried over Na₂SO₄, filtered and evaporated in vacuo. The residue
20 was dissolved in 20 ml of 80% acetic acid/water solution and was stirred until the reaction was completed. The solvent was evaporated and the residue was purified on a silica gel column, using 10-15% MeOH/CHCl₃. Fractions containing one spot by TLC (10%
25 MeOH/CHCl₃, R_f = 0.35) were pooled and evaporated to give the pure product (330 mg).

3'-O-(β -D-5-Fluoro-2'-deoxyuridinyl)-(3'-3')- α -L-5-fluoro-2'-deoxyuridine (27f) [1-122]

30 The O-protected dimer, 26f (200 mg) was treated with 20 ml of concentrated ammonia solution until the reaction is completed. The solvent was stripped off in vacuo and the residue was purified on DEAE cellulose ion exchange column using gradient of NH₄CO₃ buffer from 0.02-0.2 M. Pure fractions were evaporated at
35 40°C in high vacuo to dryness to give the pure product (79 mg).

NMR: (CD₃OD) δ = 2.45 (m, 3H), 2.69 (m, 1H), 3.67 (m, 2H), 3.75 (m, 2H), 4.13 (t, 1H), 4.65 (m, 2H), 6.19 (m, 2H), 7.98 (td, 2H).

³¹P NMR: (D₂O) δ = -1.0(s)

5 G. 9-L, β -L-5fu33 Dimer (L-113)

5'-O-Dimethoxytrityl-3'-O-(3'-O-acetyl)- β -L-5-fluoro-2'-deoxyuridinyl- α -L-5-fluoro-2'-deoxyuridine (25g)

The 3'-O-acetyl- β -D-5-fluoro-2'-deoxyuridine (0.12 g, 0.67 mmol) was dissolved in dry acetonitrile (20 ml). Sublimed 1H-tetrazole (70 mg) was added and the mixture was stirred under an argon atmosphere for 15 minutes. The solution of 21f (0.51 mg, 0.67 mmol), dissolved in 10 ml of dry acetonitrile was added via syringe to the reaction solution over 5 minutes. The mixture was allowed to stir at room temperature for three hours. The acetonitrile was evaporated in vacuo to a residue. This residue was triturated with a 70% EtOAc/ether mixture. The undissolved tetrazole was filtered off and the filtrate was evaporated to give a dry yellow foam (611 mg). This foam was used in the next step without further purification.

(3'-Acetoxy- β -L-5-fluoro-2'-deoxyuridinyl)- α -L-5-fluoro-2'-deoxyuridine cyanoethyl phosphate ester (26g)

The dimer, 25g (611 mg), was dissolved in 8 ml of THF and 2 ml of pyridine containing 0.2 ml of water. Iodine crystals (30 mg) were added and the contents of the loosely stoppered flask were allowed to stir for 1 hour. Excess iodine was discharged by the addition of few drops of saturated sodium thiosulfate. The reaction mixture was then evaporated to dryness. The crude product was in EtOAc washed with saturated NaHCO₃ solution and brine. The organic layer was dried over Na₂SO₄, filtered and evaporated in vacuo. The residue was dissolved in 20 ml of 80% acetic acid/water solution and was stirred until the reaction was completed. The solvent was evaporated and the residue was purified on a silica gel column, using 10-15%

MeOH/CHCl₃. Fractions containing one spot by TLC (10% MeOH/CHCl₃, R_f=0.35) were pooled and evaporated to give the pure product (200 mg).

5 3'-O-(8-L-5-Fluoro-2'-deoxyuridinyl)-(3'-5')-α-L-5-fluoro-2'-deoxyuridine (27g) (α-L 8-L 5FUDR Dimer, L-119)

10 The O-protected dimer, 26g (200 mg) was treated with 20 ml of concentrated ammonia solution until the reaction is completed. The solvent was stripped off in vacuo and the residue was purified on DEAE cellulose ion exchange column using gradient of NH₄CCl₃ buffer from 0.02-0.2 M. Pure fractions were evaporated at 40°C in high vacuo to dryness to give the pure product (134 mg).

15 NMR: (D₂O) δ = 2.30 (m, 3H), 2.71 (m, 1H), 3.65 (m, 2H), 4.03 (m, 2H), 4.08 (t, 1H), 4.47 (m, 1H), 4.68 (m, 2H), 6.13 (d, 1H), 6.24 (td, 1H), 7.89 (d, 1H), 7.95 (d, 1H).

20 ³¹P NMR: (D₂O) δ = 0.32(s)
5'-O-(Dimethoxytrityl)-8-L-2'-deoxyuridine-3'-N,N-diisopropylmethoxy phosphoramidite (21b)

25 The 5'-O-Dimethoxytrityl-α-L-2'-deoxyuridine (1.0 g, 1.88 mmol) was dissolved in anhydrous dichloromethane (50 ml). N,N-diisopropylethylamine (1.31 ml, 7.55 mmol) was added through a septum, followed by chloro-N,N-diisopropylmethoxyphosphine (0.55 ml, 2.83 mmol), under an argon atmosphere. The reaction was stirred for 30 minutes. The solvent was evaporated and the residue was partitioned between an 30 80% EtOAc/triethylamine mixture and brine. The organic layer was washed with saturated NaHCO₃ solution and brine. The organic residue was evaporated to dryness and the residue was purified on a silica gel column using a mixture of dichloromethane, EtOAc and 35 triethylamine (50:40:10; R_f=0.8). The product was isolated quantitatively as a yellow foam and it was used in the next step without further purification.

5'-O-Dimethoxytrityl-3'-(0-(3'-O-acetyl)-8-D-5-fluoro-2'-deoxyuridinyl)-8-L-2'-deoxyuridine methyl phosphite ester (25b)

5 The 3'-O-acetyl- β -D-5-fluoro-2'-deoxyuridine
(0.54 g, 1.88 mmol) was dissolved in dry acetonitrile
(50 ml). Sublimed 1H-tetrazole (200 mg) was added and
the mixture was stirred under an argon atmosphere for
15 minutes. The solution of 21b (1.88 mmol), dissolved
10 in 15 ml of dry acetonitrile was added via syringe to
the reaction solution over 5 minutes. The mixture was
allowed to stir at room temperature for three hours.
The acetonitrile was evaporated in vacuo to a residue.
This residue was triturated with a 70% EtOAc/ether
mixture. The undissolved tetrazole was filtered off
15 and the filtrate was evaporated to give a dry yellow
foam (1.08 g). This foam was used in the next step
without further purification.

(3'-Acetoxy-8-D-5-fluoro-2'-deoxyuridinyl)-8-L-2'-
deoxyuridine methyl phosphate ester (26b)

20 The dimer, 25b (1.08 g), was dissolved in 15 ml of
THF and 3 ml of pyridine containing 0.3 ml of water.
Iodine crystals (100 mg) were added and the contents of
the loosely stoppered flask were allowed to stir for 1
hour. Excess iodine was discharged by the addition of
25 few drops of saturated sodium thiosulfate. The
reaction mixture was then evaporated to dryness. The
crude product was in EtOAc washed with saturated NaHCO₃
solution and brine. The organic layer was dried over
Na₂SO₄, filtered and evaporated in vacuo. The residue
30 was dissolved in 25 ml of 80% acetic acid/water
solution and was stirred until the reaction was
completed. The solvent was evaporated and the residue
was purified on a silica gel column, using 10-15%
MeOH/CHCl₃. Fractions containing one spot by TLC (10%
35 MeOH/CHCl₃, R_f=0.4) were pooled and evaporated to give
the pure product (400 mg).

3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- β -L-5-2'-deoxyuridine (27b) (L-117)

The O-protected dimer, 26b (400 mg) was treated with 100 ml of methanolic ammonia solution until the reaction is completed. The solvent was stripped off in vacuo and the residue was purified on DEAE cellulose ion exchange column using gradient of NH_4CO_3 buffer from 0.02-0.2 M. Pure fractions were evaporated at 40°C in high vacuo to dryness to give the pure product (175 mg).

$^1\text{H NMR}$: (D_2O) δ = 2.40 (m, 3H), 2.61 (m, 1H), 3.80 (m, 2H), 4.10 (m, 2H), 4.18 (m, 2H), 4.55 (m, 1H), 4.80 (m, 1H), 5.85 (d, 1H), 6.30 (q, 2H), 7.85 (d, 1H), 8.06 (d, 1H).

$^3\text{P NMR}$: (D_2O) δ = 0.20 (s)

I. β -L-dC, β -D-5FUdR Dimer (L-113)

5'-O-Dimethoxytrityl-N⁴-benzoyl-2'-deoxy- β -L-cytidine (201)

N⁴-benzoyl-2'-deoxy- β -L-cytidine (0.8 g, 2.42) was dissolved in 50 ml of dry, distilled pyridine. To this solution was added 4,4'-dimethoxytrityl chloride (3.0 g, 8.85 mmol) and 4-dimethylamino pyridine (DMAP) (60 mg, 0.48 mmol). The mixture was stirred under an argon atmosphere for 16 hours. After this time, the pyridine was stripped off in vacuo. The residue was dissolved in EtOAc (100 ml). The organic layer was washed with water, saturated NaHCO_3 , and brine. The organic layer was dried over Na_2SO_4 , filtered and evaporated in vacuo to a residue which was purified on a silica gel column using 10% MeOH/ CHCl_3 . Pure fractions were pooled and evaporated to give the pure product as an off-white foam (1.49 g, (97% yield)). R_f =0.48 in 10% MeOH/ CHCl_3 .

$^1\text{H NMR}$: (CDCl_3 - d_3) δ = 2.3 (m, 1H), 2.75 (m, 1H), 3.42 (dd, 2H), 3.80 (s, 6H), 4.15 (q, 2H), 4.52 (m, 1H), 6.30 (t, 1H), 6.82 (dd, 4H), 7.2-7.6 (m, Ar), 7.85 (d, 2H), 8.32 (d, 1H), 8.76 (br s, 1H).

5'-O-(Dimethoxytrityl)-N'-benzoyl-2'-deoxy-β-L-cytidine-3'-N,N-diisopropylmethyl phosphoramidite (211)

The 5'-O-dimethoxytrityl-N'-benzoyl-2'-deoxy-β-L-cytidine (0.6 g, 0.95 mmol) was dissolved in anhydrous dichloromethane (50 ml). N,N-diisopropylethylamine (0.66 ml, 3.79 mmol) was added through a septum, followed by chloro-N,N-diisopropylmethoxyphosphine (0.28 ml, 1.42 mmol), under an argon atmosphere. The reaction was stirred for 30 minutes. The solvent was evaporated and the residue was partitioned between an 80% EtOAc/triethylamine mixture and brine. The organic layer was washed with saturated NaHCO₃ solution and brine. The organic residue was evaporated to dryness and the residue was purified on a silica gel column using a mixture of dichloromethane, EtOAc and triethylamine (60:30:10; R_f=0.8). The product was isolated quantitatively as a yellow foam and it was used in the next step without further purification.

5'-O-Dimethoxytrityl-3'-(O-(3'-O-acetyl)-β-D-5-fluoro-2'-deoxyuridinyl)-N'-benzoyl-2'-deoxy-β-L-cytidine methyl phosphite ester (251)

The 3'-O-acetyl-β-D-5-fluoro-2'-deoxyuridine (0.23 g, 0.78 mmol) was dissolved in dry acetonitrile (30 ml). Sublimed 1H-tetrazole (110 mg) was added and the mixture was stirred under an argon atmosphere for 15 minutes. The solution of 211 (0.94 mmol), dissolved in 15 ml of dry acetonitrile was added via syringe to the reaction solution over 5 minutes. The mixture was allowed to stir at room temperature for three hours. The acetonitrile was evaporated in vacuo to a residue. This residue was triturated with a 70% EtOAc/ether mixture. The undissolved tetrazole was filtered off and the filtrate was evaporated to give a dry yellow foam (0.73 g). This foam was used in the next step without further purification.

(3'-Acetoxy-β-D-5-fluoro-2'-deoxyuridinyl)-N⁴-benzoyl-2'-deoxy-β-L-cytidine methyl phosphate ester (261)

The dimer, 261 (0.73 g), was dissolved in 20 ml of THF and 4 ml of pyridine containing 0.4 ml of water. Iodine crystals (100 mg) were added and the contents of the loosely stoppered flask were allowed to stir for 1 hour. Excess iodine was discharged by the addition of few drops of saturated sodium thiosulfate. The reaction mixture was then evaporated to dryness. The crude product was EtOAc washed with saturated NaHCO₃ solution and brine. The organic layer was dried over Na₂SO₄, filtered and evaporated in vacuo. The residue was dissolved in 25 ml of 80% acetic acid/water solution and was stirred until the reaction was completed. The solvent was evaporated and the residue was purified on a silica gel column, using 10-15% MeOH/CHCl₃. Fractions containing one spot by TLC (10% MeOH/CHCl₃, R_f=0.4) were pooled and evaporated to give the pure product (108 mg).

3'-O-(β-D-5-fluoro-2'-deoxyuridinyl)-(3'-5')-2'-deoxy-β-L-cytidine (271) (L-113)

The O-protected dimer, 261 (108 mg) was treated with 100 ml of methanolic ammonia solution until the reaction is completed. The solvent was stripped off in vacuo and the residue was purified on DEAE cellulose ion exchange column using gradient of NH₄CO₃ buffer from 0.02-0.2 M. Pure fractions were evaporated at 40°C in high vacuo to dryness to give the pure product (56 mg).

¹H NMR: (D₂O) δ =

³¹P NMR: (D₂O) δ = 0.05(s)

J. β-D-5FUdR, β-L-dC Dimer (L-114)

5'-O-Dimethoxytrityl-3'-(C-(3'-O-acetyl)-N⁴-benzoyl-2'-deoxy-β-L-cytidinyl)-β-D-5-fluoro-2'-deoxyuridine cyanoethyl phosphite ester (291)

The 3'-O-acetyl-β-D-5-fluoro-2'-deoxyuridine (0.25 g, 0.67 mmol) was dissolved in dry acetonitrile

(30 ml). Sublimed 1H-tetrazole (94 mg) was added and the mixture was stirred under an argon atmosphere for 15 minutes. The solution of 21j (0.51 g, 0.67 mmol), dissolved in 15 ml of dry acetonitrile was added via syringe to the reaction solution over 5 minutes. The mixture was allowed to stir at room temperature for three hours. The acetonitrile was evaporated in vacuo to a residue. This residue was triturated with a 70% EtOAc/ether mixture. The undissolved tetrazole was filtered off and the filtrate was evaporated to give a dry yellow foam (0.49 g). This foam was used in the next step without further purification.

(3'-acetoxy-N⁴-benzoyl-2'-deoxy-β-L-cytidinyI)-β-D-5-fluoro-2'-deoxyuridinyI cyancethyl phosphate ester (26j)

The dimer, 25j (0.49 g), was dissolved in 8 ml of THF and 2 ml of pyridine containing 0.2 ml of water. Iodine crystals (30 mg) were added and the contents of the loosely stoppered flask were allowed to stir for 1 hour. Excess iodine was discharged by the addition of few drops of saturated sodium thiosulfate. The reaction mixture was then evaporated to dryness. The crude product was EtOAc washed with saturated NaHCO₃ solution and brine. The organic layer was dried over Na₂SO₄, filtered and evaporated in vacuo. The residue was dissolved in 20 ml of 80% acetic acid/water solution and was stirred until the reaction was completed. The solvent was evaporated and the residue was purified on a silica gel column, using 10-15% MeOH/CHCl₃. Fractions containing one spot by TLC (10% MeOH/CHCl₃, R_f=0.4) were pooled and evaporated to give the pure product (188 mg).

3'-O-(2'-Deoxy-β-L-cytidinyI)-(3'-5')-β-D-5-fluoro-2'-deoxyuridine (27j) (L-314)

The O-protected dimer, 26j (188 mg) was treated with 100 ml of concentrated ammonia solution until the reaction is completed. The solvent was stripped off in

vacuo and the residue was purified on DEAE cellulose ion exchange column using gradient of NH_4CO_3 buffer from 0.02-0.2 M. Pure fractions were evaporated at 40°C in high vacuo to dryness to give the pure product (105 mg).

NMR: (D_2O) δ = 2.30 (m, 3H), 2.50 (m, 1H), 3.80 (m, 2H), 4.05 (m, 2H), 4.10 (m, 2H), 4.20 (m, 1H), 4.52 (m, 1H), 4.75 (m, 1H), 6.05 (d, 1H), 6.29 (q, 2H), 7.89 (d, 1H), 9.03 (d, 1H).

^3P NMR: (D_2O) δ = 0.05(s)

K. β -D 5FUdR, α -L-dC Dimer (L-115)

5'-O-Dimethoxytrityl-3'-[O-(3'-O-acetyl)-N⁴-benzoyl]-2'-deoxy- α -L-cytidinyl]- β -D-5-fluoro-2'-deoxyuridine cyanoethyl phosphite ester (25k)

The 3'-O-acetyl- β -D-5-fluoro-2'-deoxyuridine (0.19 g, 0.51 mmol) was dissolved in dry acetonitrile (30 ml). Sublimed 1H-tetrazole (80 mg) was added and the mixture was stirred under an argon atmosphere for 15 minutes. The solution of 21k (0.45 g, 0.61 mmol), dissolved in 15 ml of dry acetonitrile was added via syringe to the reaction solution over 5 minutes. The mixture was allowed to stir at room temperature for three hours. The acetonitrile was evaporated in vacuo to a residue. This residue was triturated with a 70% EtOAc/ether mixture. The undissolved tetrazole was filtered off and the filtrate was evaporated to give a dry yellow foam (0.42 g). This foam was used in the next step without further purification.

(3'-Acetoxy-N⁴-benzoyl-2'-deoxy- α -L-cytidinyl)- β -D-5-fluoro-2'-deoxyuridinyl cyanoethyl phosphate ester (26k)

The dimer, 25k (0.42 g), was dissolved in 10 ml of THF and 2 ml of pyridine containing 0.2 ml of water. Iodine crystals (45 mg) were added and the contents of the loosely stoppered flask were allowed to stir for 1 hour. Excess iodine was discharged by the addition of few drops of saturated sodium thiosulfate. The

reaction mixture was then evaporated to dryness. The crude product was EtOAc washed with saturated NaHCO₃ solution and brine. The organic layer was dried over Na₂SO₄, filtered and evaporated in vacuo. The residue was dissolved in 25 ml of 80% acetic acid/water solution and was stirred until the reaction was completed. The solvent was evaporated and the residue was purified on a silica gel column, using 10-15% MeOH/CHCl₃. Fractions containing one spot by TLC (10% MeOH/CHCl₃, R_f=0.4) were pooled and evaporated to give the pure product (125 mg).

2'-O-(2'-deoxy-α-L-cytidinyl)-3'-5'-β-D-5-flucro-2'-deoxyuridine (27k)

The C-protected dimer, 26k (125 mg) was treated with 100 ml of concentrated ammonia solution until the reaction is completed. The solvent was stripped off in vacuo and the residue was purified on DEAE cellulose ion exchange column using gradient of NH₄CO₃ buffer from 0.02-0.2 M. Pure fractions were evaporated at 40°C in high vacuo to dryness to give the pure product (40 mg).

NMR: (D₂O) δ = 2.15 (m, 1H), 2.35 (m, 1H), 2.60 (m, 1H), 2.71 (m, 1H), 3.81 (m, 2H), 3.97 (m, 2H), 4.22 (m, 1H), 4.52 (m, 2H), 6.02 (d, 1H), 6.15 (dd, 1H), 6.28 (t, 1H), 7.87 (d, 1H), 8.03 (d, 1H).

P³¹NMR: (D₂O) δ = -0.12(s)

Example 5

Dimers Testing in vitro in B16 Melanoma and P388 Leukemia and in Inhibition Assays Against 293 Processive Telomerase

The biological effects of the dimers were compared with those of the monomeric 5-FUdR on P388 leukemia and B16 melanoma cell lines and in inhibition assays against 293 processive telomerase. Telomerase is a DNA-processive enzyme that is not expressed in normal somatic cells but generally only in germ-line cells and fetal cells. In many types of cancer cells, enzyme

activity is reactivated, and others, telomerase inhibitors can therefore serve as a valuable new class of antineoplastic agents. The results are shown in Table 2.

5 Table 2 - Inhibition of Tumor Cell Growth and Telomerase Activity by 5-FUdR Dinucleoside Monophosphates

Compound	Growth Inhibition IC ₅₀ (nM)		Telomerase Inhibition (Mean±SEM) % at 1 nM
	P388	B16	
β-D FUDR	2.8	28	0
α-L, β-D Dimer	0.57	2.45	84±11
α-L FUDR	NT	389,500	NT

NT = Not Tested

15 The results indicate that the prototype dimers inhibit the growth of murine-cultured leukemic P388 and melanoma B16 cells with great potency (some IC₅₀ values of less than 1 nM.) The IC₅₀ values are several times more potent than FUDR. These results are unexpected and thus these compounds are truly unique.

20 The preliminary results of the telomerase inhibition are also intriguing. The α-L, β-D dimer inhibited the enzyme by 84% compared to control.

25 These data indicate that dimers containing an L-sugar have extremely interesting biological profiles and represent a novel class of potent antineoplastic agents. The activity profile of the L-dimers is different from that of the parent monomeric drug β-D-5FUDR.

30 The biological effects of the dimers were compared with those of the monomeric 5-FUDR on P388 leukemia and B16 melanoma cell lines. The results are shown in Table 3.

Table 3 - In Vitro Testing Data

CODE #	COMPOUND	IC50 (nM)		
		L1210	P388	B16
L-101	β -D-FUdR, β -D-FUdR	0.45	0.52	2.6
L-102	β -D-FUdR, α -L-FUdR	0.71	---	3.0
L-103	α -L-FUdR, β -D-FUdR	0.41	0.57	2.45
L-107	α -L-dU, β -D-FUdR	NT	1.2	18.0
L-108	α -L-FUdR, α -L-FUdR	NT	22,200	52,200
L-109	β -L-FUdR, β -L-FUdR	NT	5860	45,900
L-110	β -L-FUdR, β -D-FUdR	NT	2.0	6.3
L-111	α -L-dC, β -D-FUdR	NT	0.7	5.0
L-112	α -L-FUdR, β -D-FUdR (5', 5')	NT	56	NT
L-113	β -L-dC, β -D-FUdR	NT	95	52
L-115	β -D-FUdR, α -L-dC	NT	125	20
L-117	β -L-dU, β -D-FUdR	NT	<90	5
L-119	α -L-FUdR, β -L-FUdR	NT	240	NT
L-122	α -L-FUdR, β -L-FUdR (3', 3')	NT	175	NT
L-124	β -D-FUdR, α -L-dU	NT	1190	NT
L-126	α -L-dT, β -D-FUdR	NT	104	NT
L-128	α -L-FUdR, β -D-FUdR (phosphorothioate)	NT	90	170

These data indicate that the dinucleoside monophosphate compounds containing β -D-5FUdR in conjunction with α -L or β -L-nucleosides show superior in vitro activities against murine P388 leukemia and B16 melanoma cell lines, as is evidenced by lower IC₅₀ values. This indicates that such nucleoside dimers may indeed be acting by mechanisms different from those of 5-FUdR or are metabolized and/or transported differently from 5-FUdR.

5-FUdR or are metabolized and/or transported differently from 5-FUdR.

Example 6

5 Determination of Thymidylate Synthetase Activity And Its Inhibition In Intact L1210 Leukemia Cells In Vitro

The mouse leukemia L1210 cells are harvested from the cell culture flasks and the cell concentration is determined. The cells are then resuspended in the desired amount of the medium to give a stock concentration 5×10^7 cells/mL. Series of the dilution of the stock solution of the compounds to be tested are prepared (concentrations are ranged from 10^8 M to 10^{-3} M). The solution of the compound to be tested in the desired concentration is pipetted into a microcentrifuge tube and incubated at 37°C using a shaking water bath. The reaction is started by addition of $[5\text{-}^3\text{H}]\text{-2'-deoxycytidine}$ ($10\text{ }\mu\text{L}$, concentration of the stock solution - 10^{-3} M) after a 30 or 60 min. preincubation with $80\text{ }\mu\text{L}$ of the cell suspension and allowed to proceed for 30 min. in a shaking water bath at 37°C . The reaction is terminated by adding $100\text{ }\mu\text{L}$ of the 10% charcoal in 4% HClO_4 . The tubes are vigorously stirred by vortexing and then centrifuged for 10 min. in a Beckman Microfuge. The radioactivity of a $100\text{ }\mu\text{L}$ of supernatant fraction from each tube is counted in a Packard Tri-Carb (model 2450 or 3255) liquid scintillation spectrometer using a toluene based scintillation mixture. The release of tritium is expressed as a percentage of the total amount of radioactivity added. IC_{50} values determined from dose response curves represent the concentration of inhibitors required for 50% inhibition of the release of tritium. Table 4 below shows the results of the analysis of tritium release and determination of the IC_{50} .

TABLE 4

Sample Code	Inhibition of Tritium Release, IC ₅₀ (μM)
5FUdR	0.035
L-102	0.035
L-103	0.035
L-107	> 100
L-108	> 100
L-109	> 100
L-110	5
L-111	N/T

Example 7

In Vivo Testing of Dimers in P388 Leukemia B16 MelanomaA. EXPERIMENTAL1. P388 Leukemia

B6D2F1 mice received i.p. inocula of P388 murine leukemia cells prepared by removing ascites fluid containing P388 cells from tumored B6D2F1 mice, centrifuging the cells, and then resuspending the leukemia cells in saline. Mice received 1×10^6 P388 cells i.p. on day 0. On day 1, tumored mice were treated with the dimers or vehicle control. The route of drug administration was i.p. and the schedule selected was daily x 5. The maximum tolerated doses (MTD) was 200 mg/kg for each dimer and was determined in initial dose experiments in non-tumored mice. In the actual experiments, L-103 was given at 100 mg/kg and 50 mg/kg.

2. B16 Melanoma

B6D2F1 mice received i.p. inocula of B16 murine melanoma brei prepared from B16 tumors growing s.c. in mice (day 0). On day 1, tumored mice were treated with the dimers or vehicle control. The route of drug administration was i.p. and the schedule selected was

daily x 5. The maximum tolerated doses (MTD) was 200 mg/kg for each dimer and was determined in initial dose experiments in non-tumored mice. In the actual experiments, L-103 was given at 100 mg/kg and 50 mg/kg.

5 3. Survival Standard

The mean survival times of all groups were calculated, and results are expressed as mean survival of treated mice / mean survival of control mice (T/C) x 100%. A T/C value of 150 means that the mice in the treated group lived 50% longer than those of the control group; this is sometimes referred to as the increase in life span, or ILS value.

10 In the P388 studies mice that survive for 30 days are considered long term survivors or cures while in B16, mice that survive for 60 days are considered long term survivors or cures. The universally accepted cut-off for activity in both models, which as been used for years by the NCI, is T/C = 125. Conventional use of B16 and P388 over the years has set the following levels of activity: T/C < 125, no activity; T/C = 125-150, weak activity; T/C = 150-200, modest activity; T/C = 200-300, high activity; T/C > 300, with long term survivors; excellent, curative activity.

B. RESULTS

25 1. P388 Leukemia

L-103 demonstrated modest activity in the P388 leukemia in mice at all doses tested (Table 5). L-103 gave i.p. daily x 5 at doses of 100 mg/kg and 50 mg/kg resulted in T/C values of 149 and 144 respectively. Fluorodeoxyuridine (FUDR) was used as the positive drug control in this study; FUDR produced a T/C = 164 in the P388 test (Table 5). All agents were well-tolerated in this experiment; there was little or no body weight loss and no toxic deaths were recorded.

TABLE 5
L-103 vs. Murine P388 Leukemia

Group	n	Dose	Weight Change (Day 7)	T/C
Control	(10)	0.9% Saline	+9.1%	100
L-103	(10)	100 mg/kg	+1.5%	149
L-103	(10)	50 mg/kg	-1.6%	144
FUdR	(10)	100 mg/kg	-2.7%	164

2. B16 Melanoma

L-103 demonstrated modest activity against B16 melanoma implanted in mice (Table 6). L-103 (i.p.; daily x 5) gave T/C values of 139 and 134 respectively. The positive control drug FUdR resulted in modest efficacy in the B16 test; a T/C value of 135 was obtained (Table 6). All agents were well-tolerated, with little or no weight loss; no drug-related deaths occurred.

TABLE 6
L-103 vs. Murine B16 Leukemia

Group	n	Dose	Weight Change (Day 7)	T/C
Control	(10)	0.9% Saline	+4.9%	100
L-103	(10)	100 mg/kg	+2.3%	139
L-103	(10)	50 mg/kg	+6.3%	134
FUdR	(10)	100 mg/kg	-0.5%	135

L-103 demonstrated modest activity against both the P388 and B16 experimental murine tumors at the two doses tested. L-103 was approximately as active as the

positive control drug FUdR in the B16 test, and was somewhat less active than FUdR in the P388 test.

From the foregoing, the significance of L-sugar-based α - and β -enantiomeric nucleosides, nucleotides and their analogues as versatile, highly effective chemotherapeutic agents is apparent. Our results on derivatives of 5-FUdR show that L-5-FUdR-containing isomers are less toxic than those containing β -D-5FUdR, perhaps because they are not phosphorylated or transported as the latter. We have found that dimeric derivatives designed and prepared from α -L-5FUdR show very potent activity against P388 leukemia cells and B16 melanoma cell lines, exceeding that of β -D-5FUdR. They appear to have unusual mechanisms of action, including inhibition of telomerase.

Example 8
Effectiveness of Dimers in Tumors

Table 7. Evaluation of the L-Nucleoside Dimers in Human Tumor Cell Lines

Compound Code	Colon HT-29 IC ₅₀ (nM)	Pancreas MiaPaCa IC ₅₀ (nM)	Prostate MCF-7 IC ₅₀ (nM)	Prostate DU145 IC ₅₀ (nM)	Prostate LNCap %Inhib.*	Prostate PC-3 %Inhib.*
L-102	NT	99	NT	140	NT	NT
L-103	NT	NT	NT	NT	NT	NT
L-107	>1000	40	634	466	NT	40
L-111	>1000	38	620	450	>30	>30
L-113	50	38	NT	130	NT	NT
L-116	9	362	525	330	>40	>40
L-117	18	36	540	69	>50	>40
L-125	35	500	660	210	>40	>40
L-126	35	33	550	200	NT	NT
L-133	NT	NT	NT	NT	>40	/>40
L-134	NT	NT	NT	NT	NT	NT
L-135	NT	NT	NT	NT	NT	>40
FUdR	4	20	450	160	>50	>40

NT = Not Tested

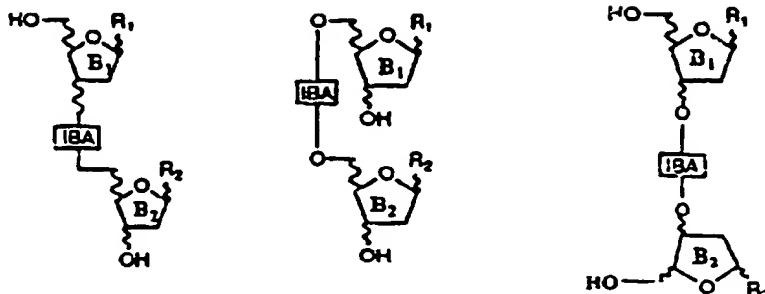
*Cells were exposed to 4 different drug concentrations: 20, 50, 75 and 100 nM. In each assay, cells were treated with drug three times (on day 1, 2 and 3). The test was a dye assay for survival of cells using Alamo Blue. Data are presented as % growth inhibition compared to control without drug at 100 nM.

All patents and publications mentioned in the specifications are indicative of the levels of those skilled in the art to which the invention pertains. All patents and publications are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

One skilled in the art readily appreciates that the patent invention is well adapted to carry out the objectives and obtain the ends and advantages mentioned as well as those inherent therein. Dimers, pharmaceutical compositions, treatments, methods, procedures and techniques described herein are presently representative of the preferred embodiments and are intended to be exemplary and are not intended as limitations of the scope. Changes therein and other uses will occur those skilled in the art which are encompassed within the spirit of the invention or defined by the scope of the pending claims.

What is claimed is:

1. A compound of the formulae:



I

II

III

or a pharmaceutically acceptable salt thereof,

5 wherein:

B₁ and B₂ are each selected from the group consisting of β-D, β-L and α-L nucleosides and wherein at least one of B₁ or B₂ must be β-L or α-L nucleoside.

10

R₁ and R₂ are selected from the group of pyrimidine bases consisting of cytosine, thymine, uracil, adenine, guanine, inosine, 5 fluorouridine (5 FUDR) and other 5-halo bases; and wherein R₁ and R₂ can be the same or a different base or alkoxy group and wherein when B₁ or B₂ is attached to the internucleotide binding agent (IBA) at the 5' position and said B₁ or B₂ is β-L or α-L then the R₁ or R₂ attached to said base cannot be cytosine; and

20

IBA is selected from the group consisting of phosphodiester, phosphorothioate, methoxy phosphotriesters, methylphosphonates, phosphoro-

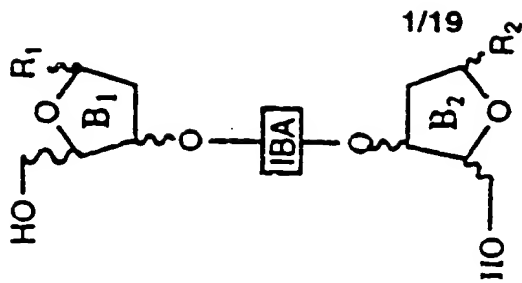
dithioates, phosphorothioates, silyl ethers, sulphonates and ethylenedioxy ethers.

2. The compound of claim 1 wherein said compound is selected from the group consisting of 3'-O-(α -L-5-fluoro-2'-deoxyuridinyl)-(3'-5')- β -D-5-fluoro-2'-deoxyuridine (L-102), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- α -L-5-fluoro-2'-deoxyuridine, (L-103), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- α -L-2'-deoxyuridine, (L-107), 3'-O-(α -L-5-fluoro-2'-deoxyuridinyl)-(3'-5')- α -L-5-fluoro-2'-deoxyuridine, (L-108), 3'-O-(α -L-5-fluoro-2'-deoxyuridinyl)-(3'-5')- β -L-5-fluoro-2'-deoxyuridine, (L-109), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- β -L-5-fluoro-2'-deoxyuridine, (L-110), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- α -L-2'-deoxycytidine, (L-111), 5'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(5'-5')- α -L-5-fluoro-2'-deoxyuridine (L-112), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')-2'-deoxy- β -L-cytidine, (L-113), 3'-O-(2'-deoxy- β -L-cytidinyl)-(3'-5')- β -D-5-fluoro-2'-deoxyuridine (L-114), 3'-O-(2'-deoxy- α -L-cytidinyl)-(3'-5')- β -D-5-fluoro-2'-deoxyuridine (L-115), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- β -L-2'-deoxyuridine (L-117), 3'-O-(β -L-2', 3'-dideoxycytidinyl)-(3'-5')- β -D-5-fluoro-2'-deoxyuridine (L-118), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- α -L-2', 3'-dideoxycytidine (L-120), 3'-O-(β -L-5-fluoro-2'-deoxyuridinyl)-(3'-5')- α -L-5-fluoro-2'-deoxyuridine (L-119), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-3')- α -L-5-fluoro-2'-deoxyuridine (L-122), 3'-O-(β -L-2'-deoxyuridinyl)-(3'-5')- β -D-5-fluoro-2'-deoxyuridine (L-124), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- α -L-2'-deoxyadenosine (L-125), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- α -L-thymidine (L-126), 3'-

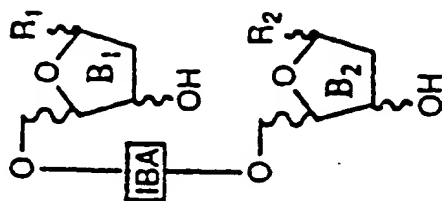
- O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- β -L-5-fluoro-2'-deoxyuridine phosphorothic acid (L-128), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- β -L-2'-deoxyguanosine (L-133), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- α -L-2'-deoxyguanosine (L-134), 3'-O-(β -L-5-fluoro-2'-deoxyuridinyl)-(3'-5')-methoxy-2-deoxyribose (L-136), 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- α -L-2'-deoxyadenosine (L-138) and 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- β -L-1-methoxy-2-deoxyribose (L-142) or a therapeutically acceptable salt thereof.
3. The compound of claim 1, wherein the formulae is I, B₁ is β -D, B₂ is α -L, R₁ and R₂ are both 5-FuDR, and IBA is a phosphodiester.
4. The compound of claim 1, wherein the formulae is II, B₁ is α -L, B₂ is β -D, R₁ and R₂ are both 5-FuDR and INB is a phosphodiester.
5. The compound of claim 1, wherein the compound is 3'-O-(β -L-5-fluoro-2'-deoxyuridinyl)- α -L-5-fluoro-2'-deoxyuridine, (L-103).
6. The compound of claim 1, wherein the compound is 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- β -L-5-fluoro-2'-deoxyuridine, (L-110).
7. The compound of claim 1, wherein the compound is 3'-O-(β -D-5-fluoro-2'-deoxyuridinyl)-(3'-5')- β -L-2'-deoxyuridine, (L-117).
8. A pharmaceutical composition comprised of a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one compound of claim 1 or 2.

9. A method of treating cancer in a mammal comprising the step of administering to said mammal bearing a cancer a therapeutically effective amount of at least one compound of claim 1 or 2.
- 5 10. A method of treating cancer in a mammal comprising the step of administering to said mammal bearing a cancer, a cancer inhibiting amount of at least one of the compounds of claim 1 or 2.
- 10 11. A method of treating a parasitic or a viral infection in a mammal comprising the step of administering to said mammal having the parasitic or viral disease, a therapeutically effective amount of at least one compound of claim 1 or 2.

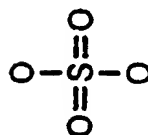
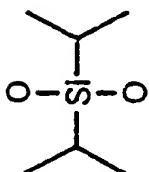
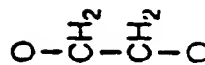
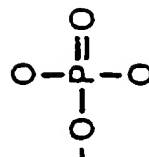
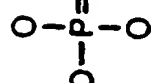
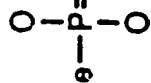
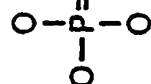
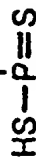
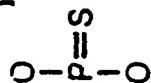
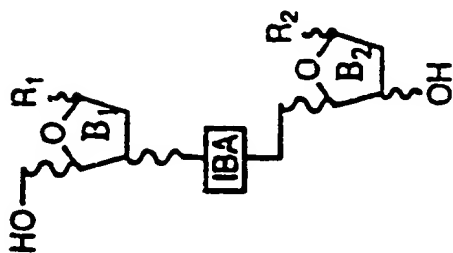
3'-3' IBA Compounds



5'-5' IBA Compounds



3'-5' IBA Compounds



where [IBA] =

Figure 1
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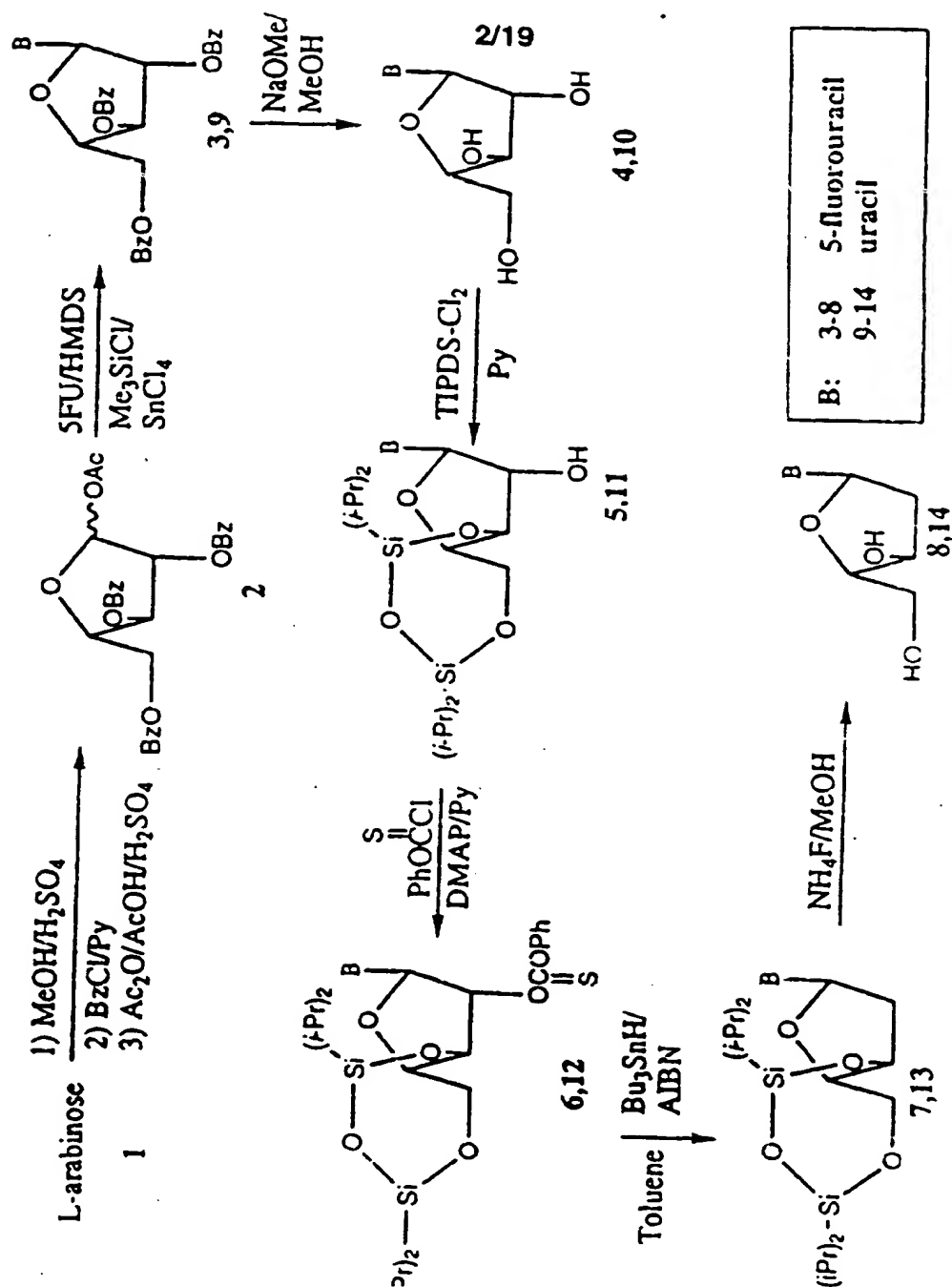


Figure 2A

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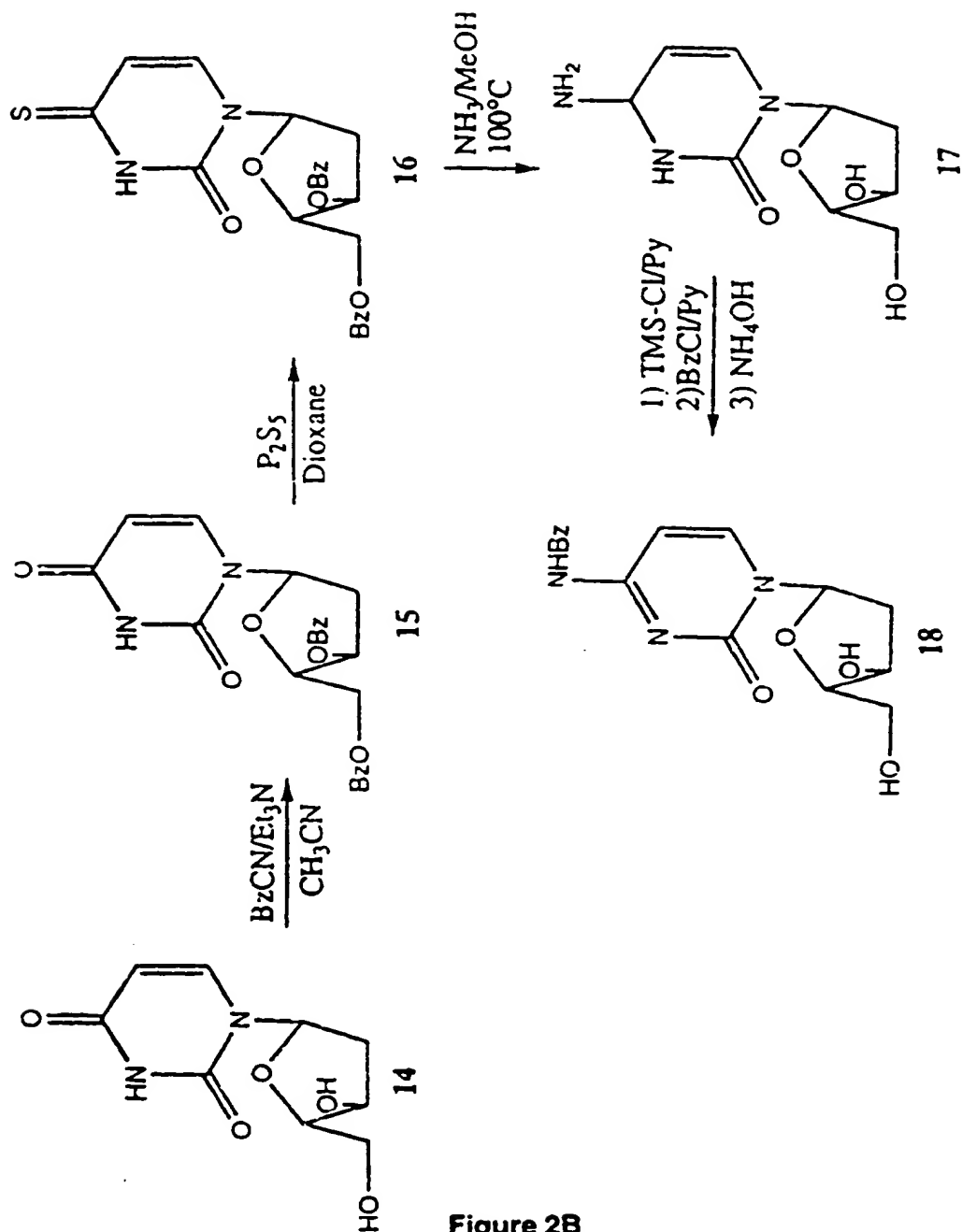


Figure 2B
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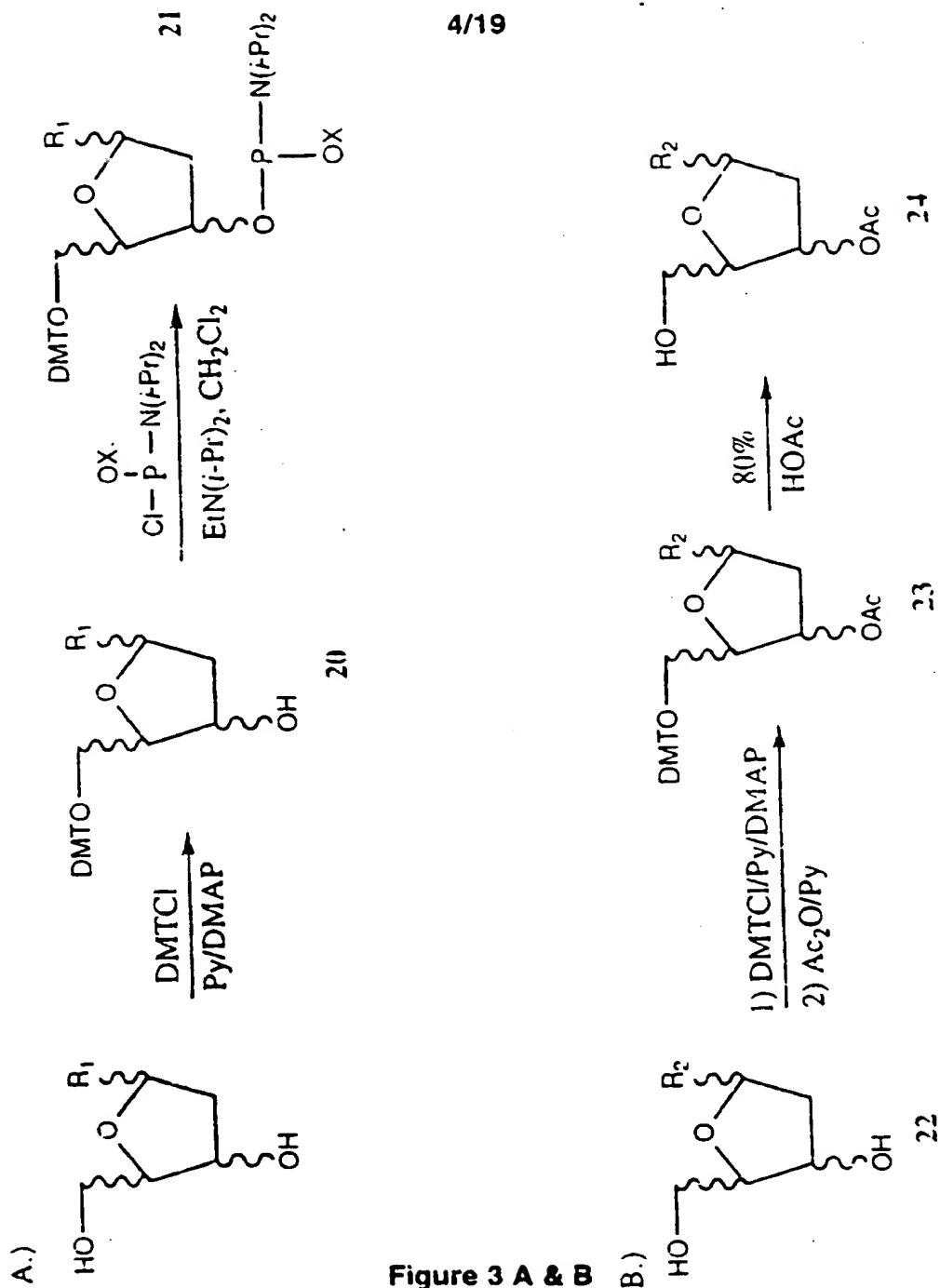


Figure 3 A & B
SUBSTITUTE SHEET (RULE 26)

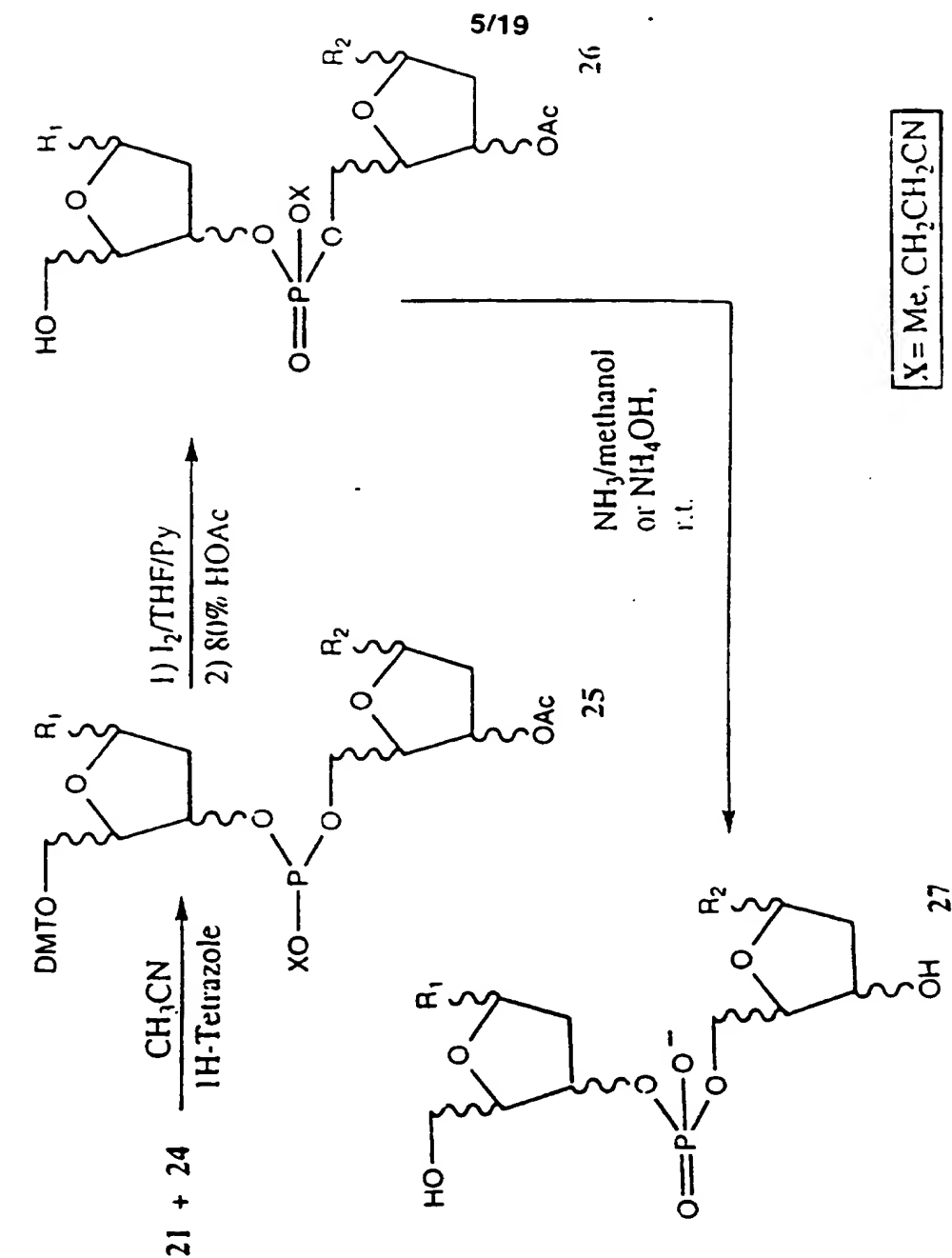


Figure 3C

SUBSTITUTE SHEET (RULE 26)

C.)

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- Series:
- a $R_1 = \alpha\text{-L-5-fluorouracil}$, $R_2 = \beta\text{-D-5-fluorouracil}$
 - b $R_1 = \beta\text{-D-5-fluorouracil}$, $R_2 = \alpha\text{-L-5-fluorouracil}$
 - c $R_1 = \alpha\text{-L-uracil}$, $R_2 = \beta\text{-D-5-fluorouracil}$
 - d $R_1 = \beta\text{-L-5-fluorouracil}$, $R_2 = \beta\text{-L-5-fluorouracil}$
 - e $R_1 = \beta\text{-L-5-fluorouracil}$, $R_2 = \beta\text{-D-5-fluorouracil}$
 - g $R_1 = \alpha\text{-L-5-fluorouracil}$, $R_2 = \beta\text{-L-5-fluorouracil}$
 - h $R_1 = \beta\text{-L-uracil}$, $R_2 = \beta\text{-D-5-fluorouracil}$
 - i $R_1 = \beta\text{-L-cytosine}$, $R_2 = \beta\text{-D-5-fluorouracil}$
 - j $R_1 = \beta\text{-D-5-fluorouracil}$, $R_2 = \beta\text{-L-cytosine}$
 - k $R_1 = \beta\text{-D-5-fluorouracil}$, $R_2 = \alpha\text{-L-cytosine}$
 - m $R_1 = \alpha\text{-L-adenosine}$, $R_2 = \beta\text{-D-5-fluorouracil}$
 - n $R_1 = \beta\text{-D-5-fluorouracil}$, $R_2 = \beta\text{-L-uracil}$
 - p $R_1 = \alpha\text{-L-thymine}$, $R_2 = \beta\text{-D-5-fluorouracil}$
 - q $R_1 = \alpha\text{-L-guanine}$, $R_2 = \beta\text{-D-5-fluorouracil}$
 - s $R_1 = \beta\text{-D-1-OMe.ribose}$, $R_2 = \beta\text{-L-5-fluorouracil}$
 - t $R_1 = \beta\text{-L-1-OMe.ribose}$, $R_2 = \beta\text{-D-5-fluorouracil}$

Figure 3 (continued)
SUBSTITUTE SHEET (RULE 26)

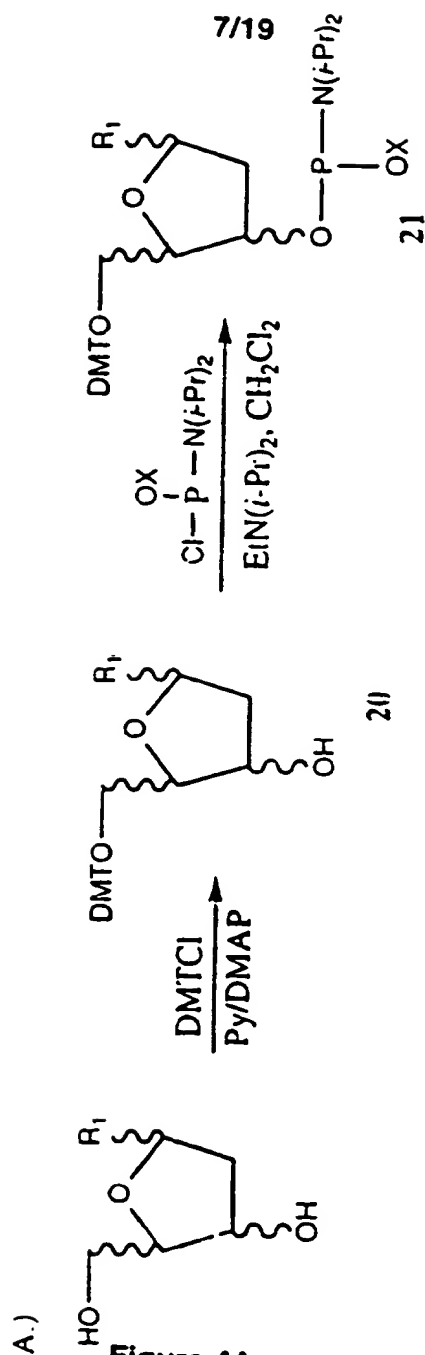


Figure 4A
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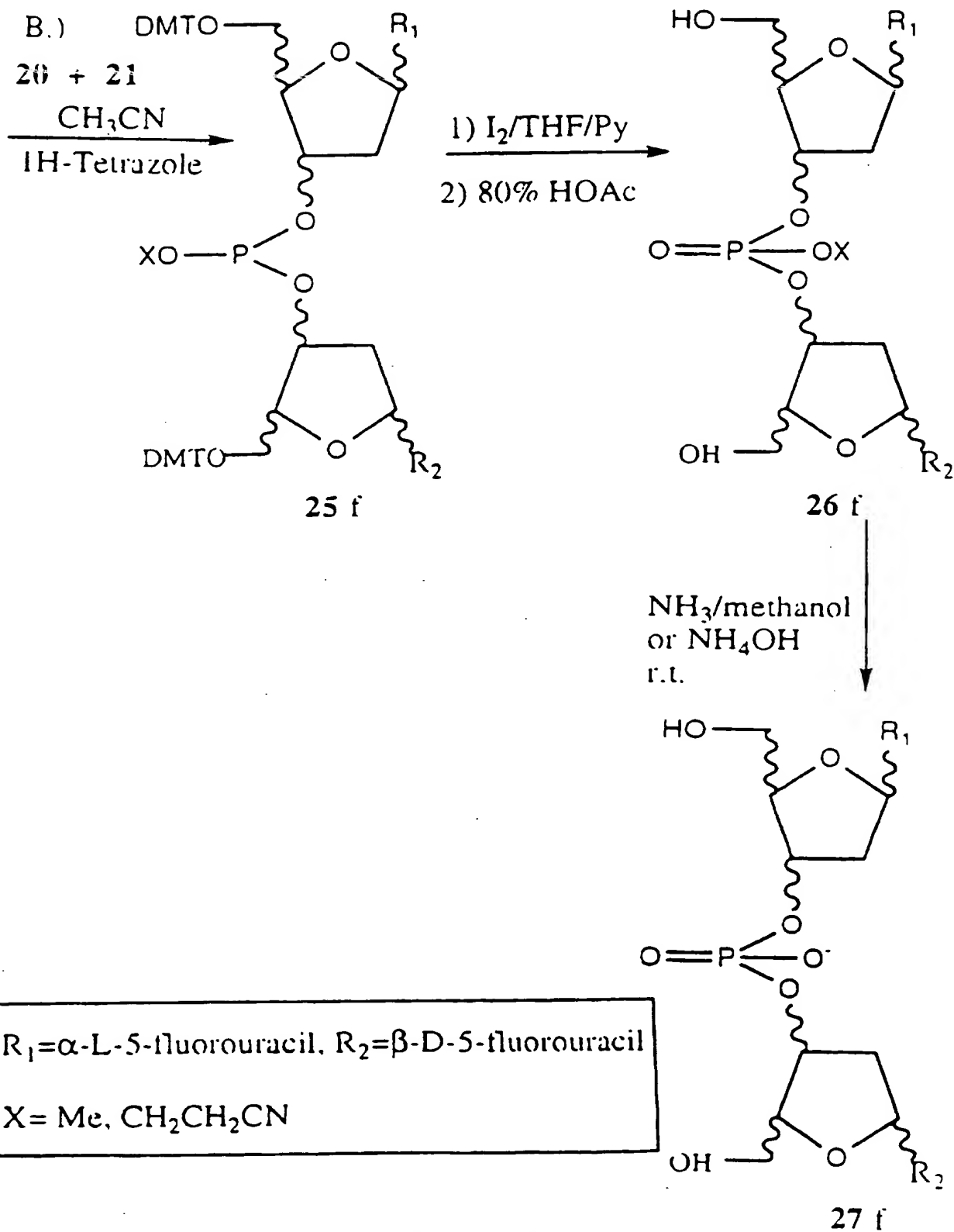


Figure 4B
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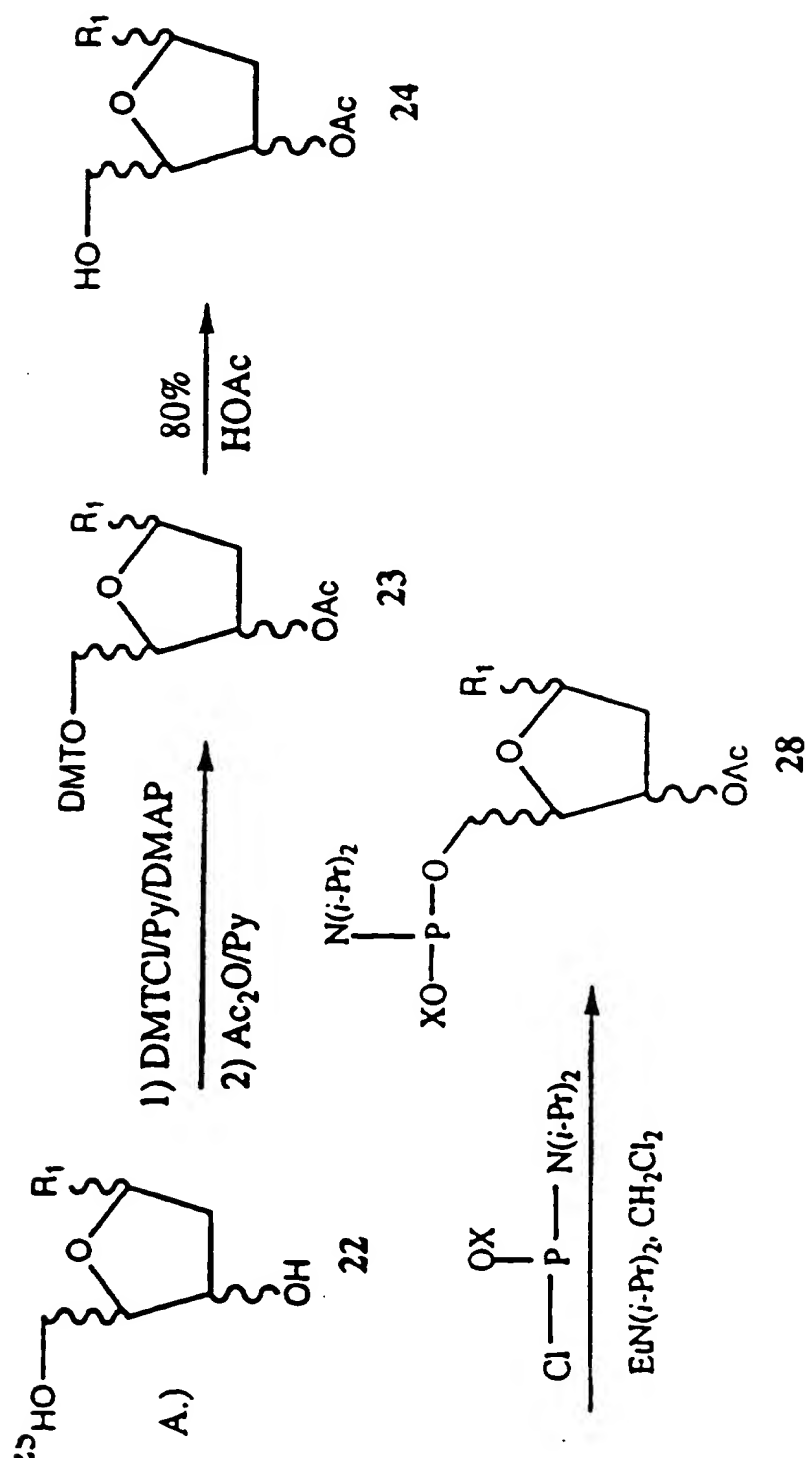


Figure 5A
SUBSTITUTE SHEET (RULE 26)

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B.) $24 + 28$

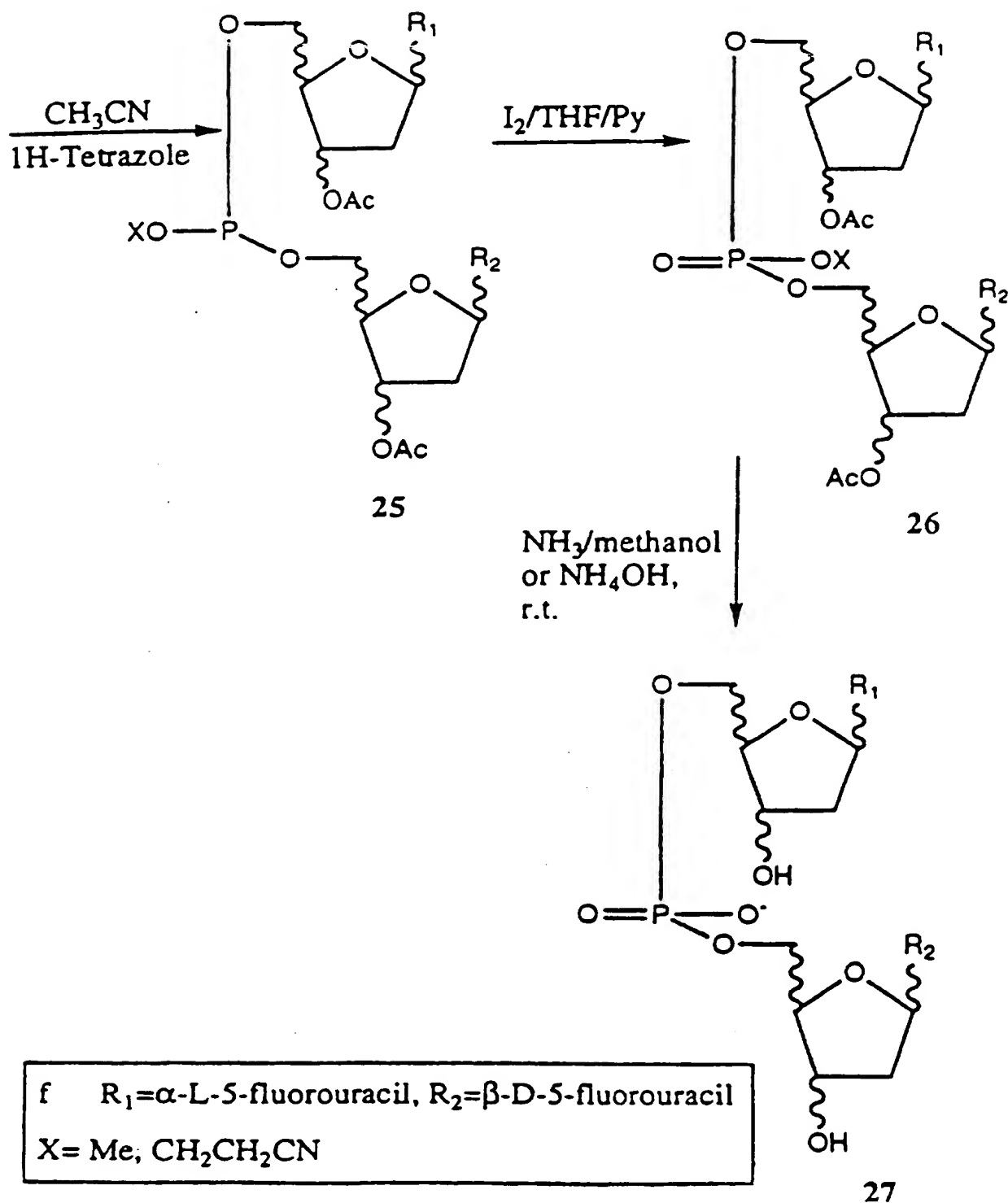


Figure 5B
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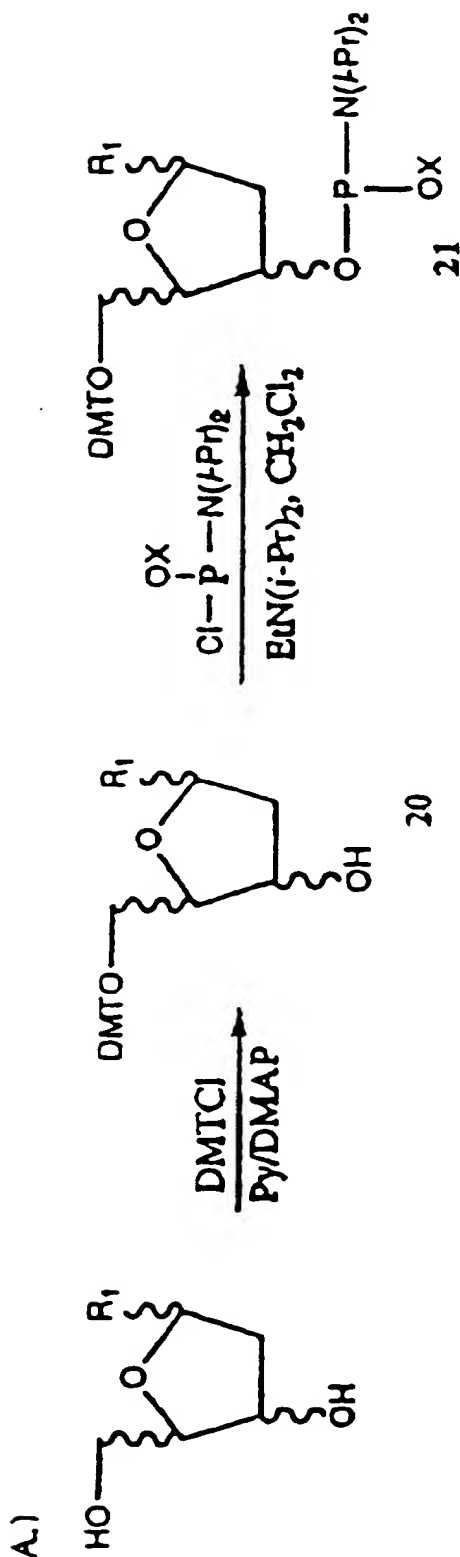


Figure 6A

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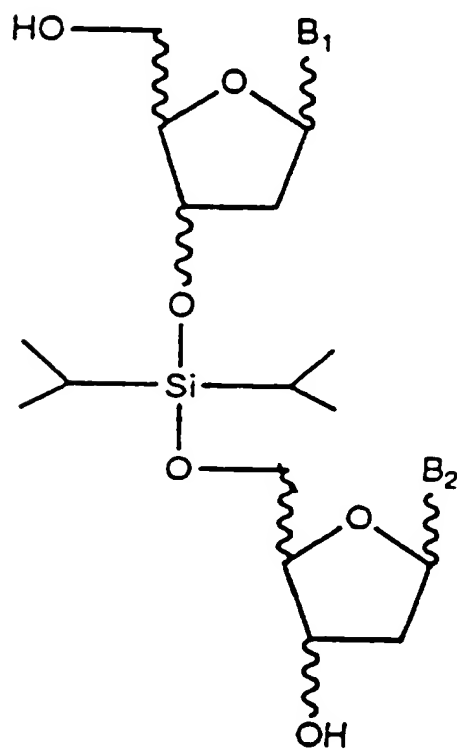
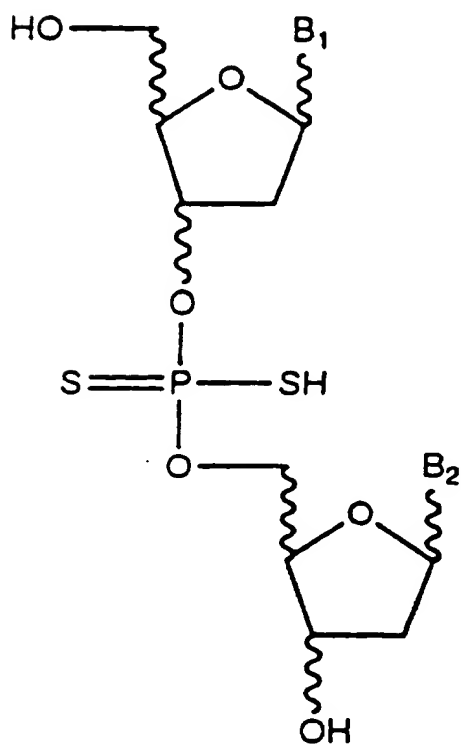
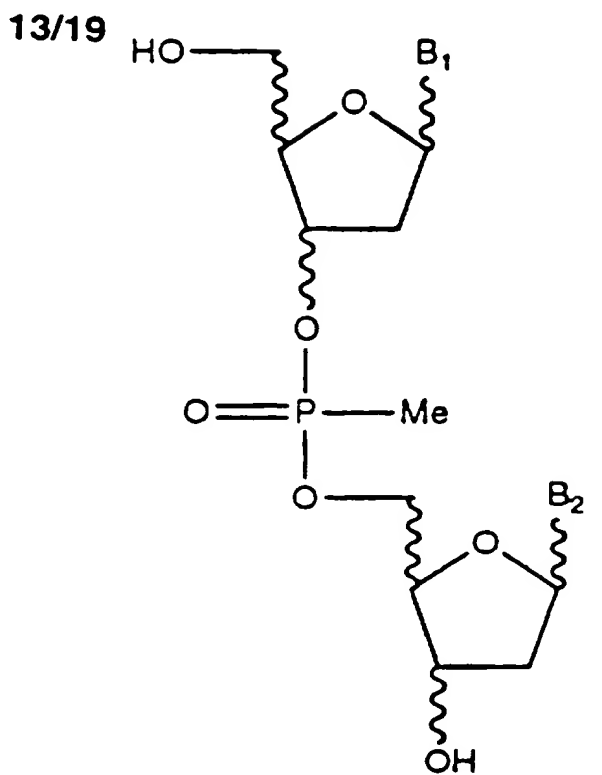
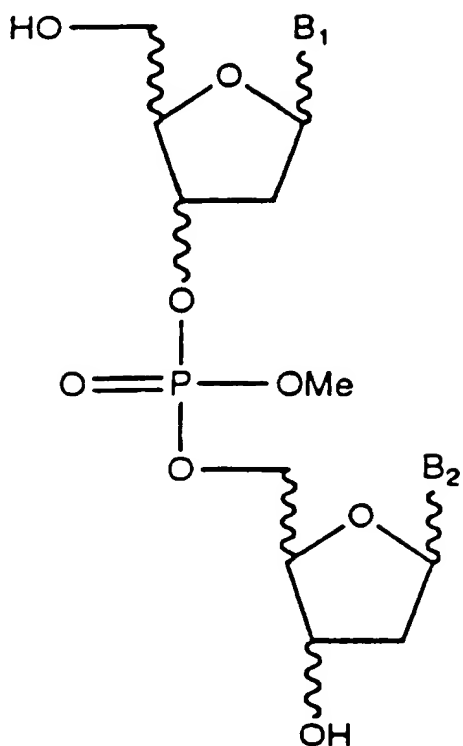


Figure 7A

SUBSTITUTE SHEET (RULE 26)

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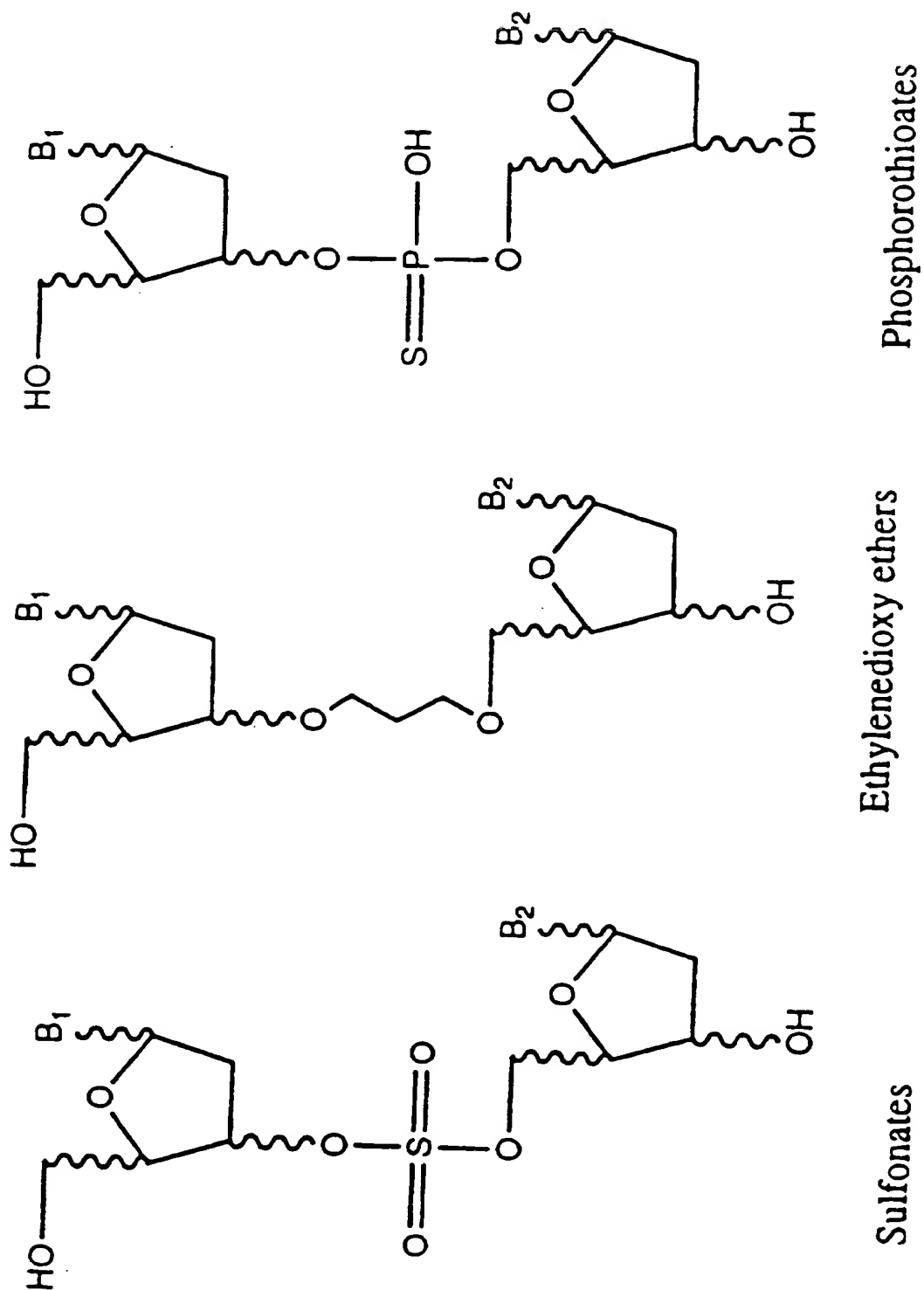
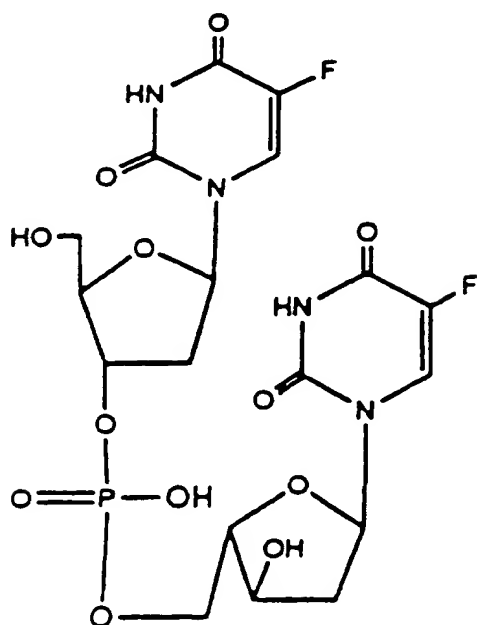


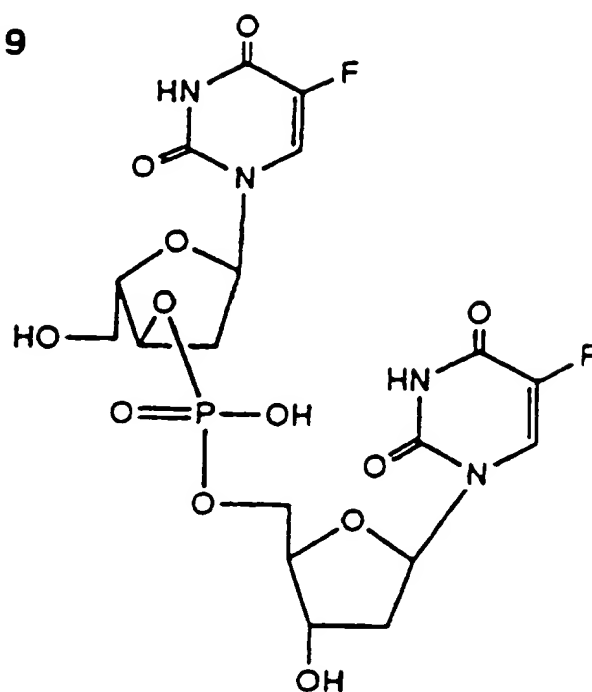
Figure 7B

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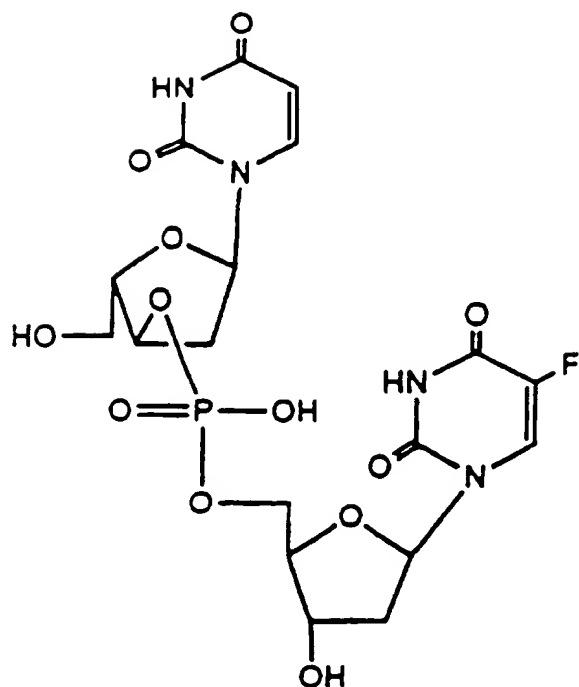


L-102

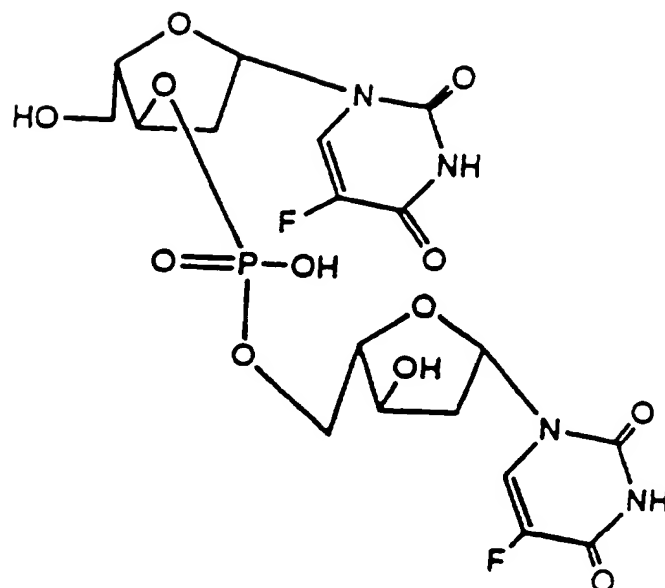
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L-103



L-107



I-109

Figure 8A
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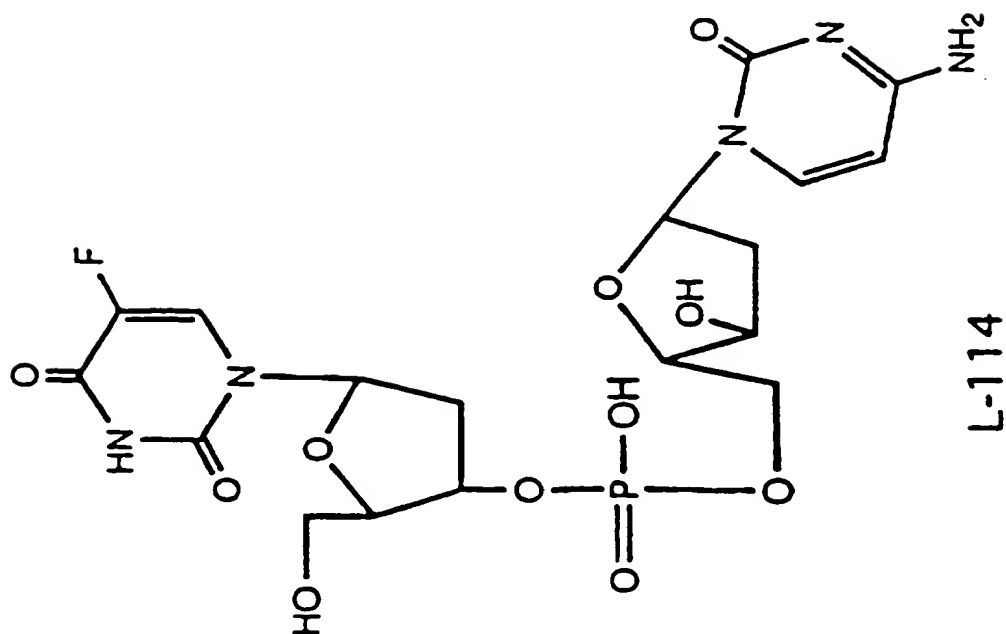
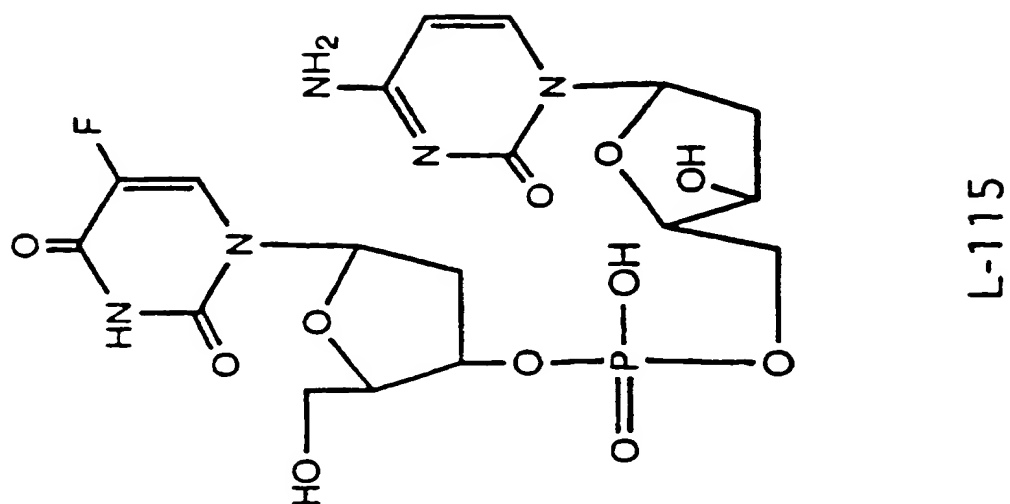


Figure 8B (continued)

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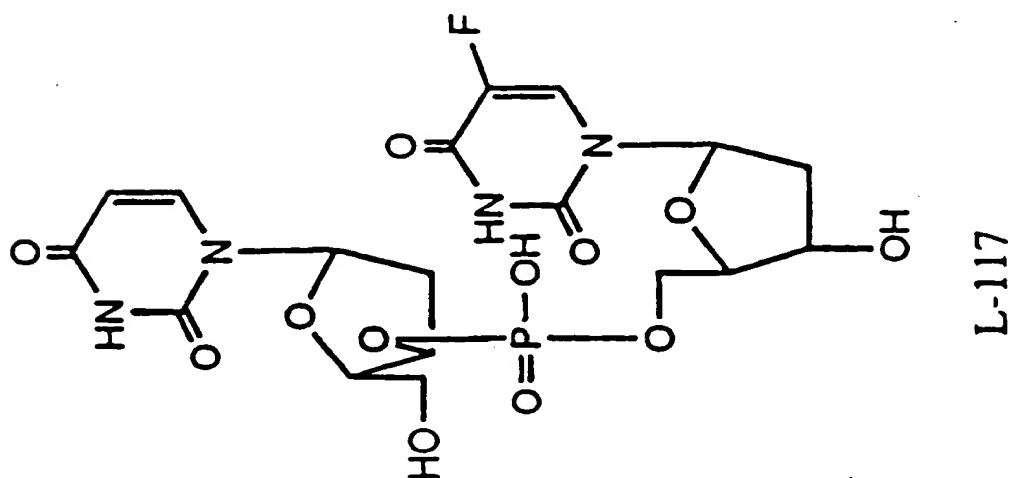
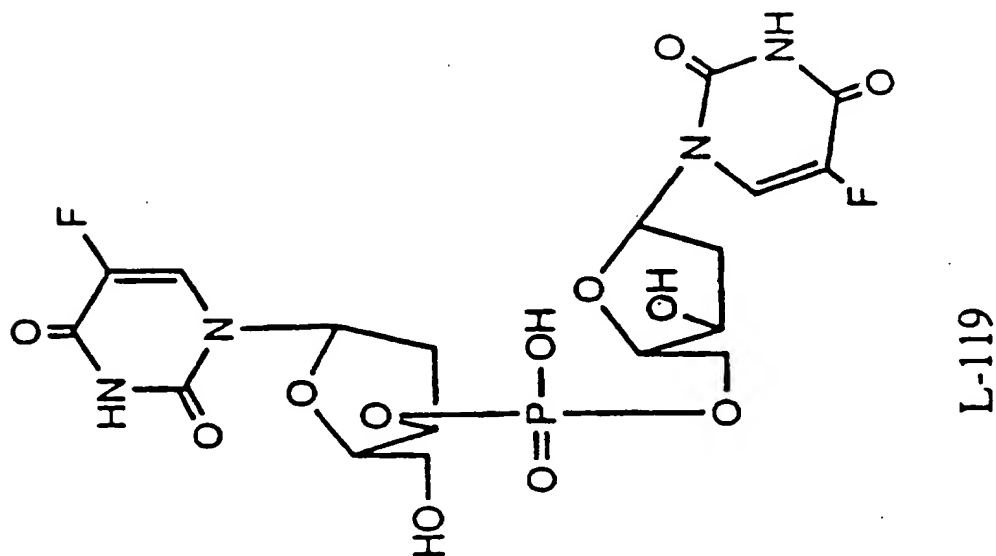
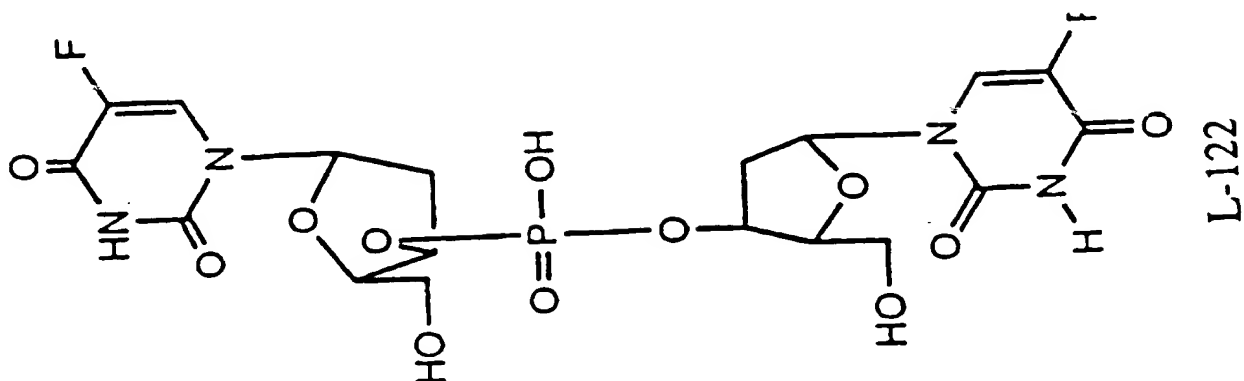


Figure 8C

SUBSTITUTE SHEET (RULE 26)

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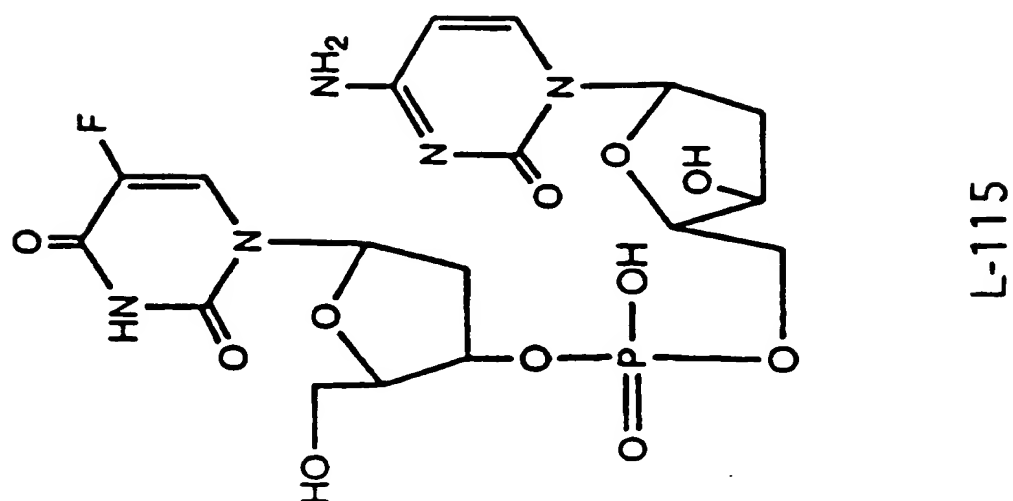
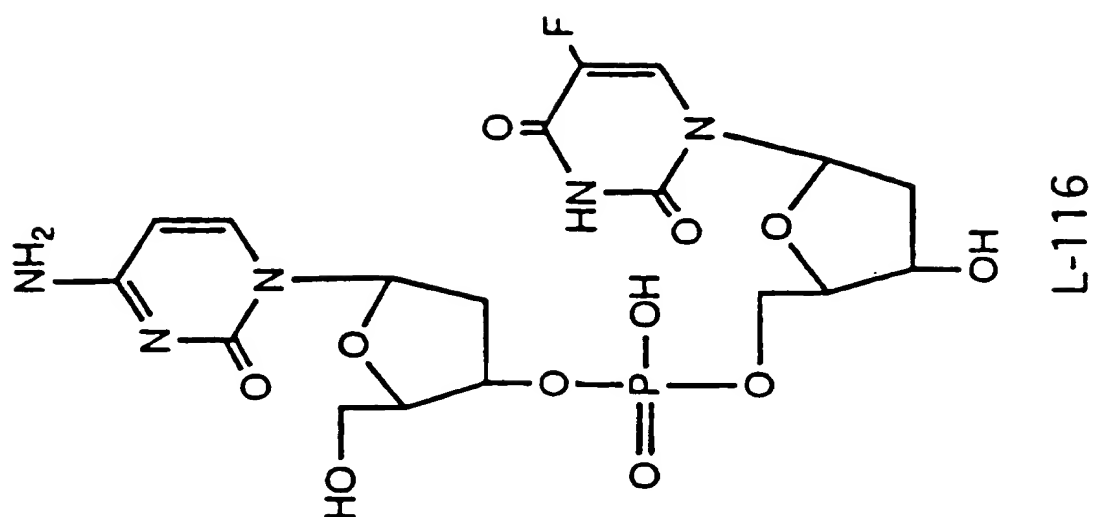


Figure 8D
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/15115**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : C07H 21/00, 23/00; A61K 31/76, 31/695

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/22.1, 23.1, 26.7, 27.6, 27.81, 28.5, 28.52, 28.54, 28.55; 514/46, 51, 63, 885

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS on line

CAS on line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, E	US 5,559,101 A (WEIS ET AL.) 24 September 1996, see entire document.	1-11
A, E	US 5,561,120 A (LIN ET AL.) 01 October 1996, see entire document.	1-11
A, E	US 5,565,438 (CHU ET AL.) 15 October 1996, see entire document.	1-11



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	* T	later document published after the international filing date or priority date and not in conflict with the application but cited to underpin the principle or theory underlying the invention
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* E	* X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
* L		document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
* O	* Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
* P	* A	document published prior to the international filing date but later than the priority date claimed
		document member of the same patent family

Date of the actual completion of the international search

18 OCTOBER 1996

Date of mailing of the international search report

07 JAN 1997

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

JAMES O. WILSON

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/15115

A. CLASSIFICATION OF SUBJECT MATTER:
US CI

US CL :

536/22.1, 23.1, 26.7, 27.6, 27.81, 28.5, 28.52, 28.54, 28.55; 514/46, 51, 63, 885

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